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ACUTE ORAL AND INTRAPERITONEAL TOXICITY
STUDY OF WR242511 AND WR269410 IN MICE

Sponsor: U.S. Army Medical Materiel
and Development Activity

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Test Articles: WR242511 Tartrate
WR269410

Study Director

Barry S. Levine, D.Sc., D.A.B.T.

In-Life Phase Completed On

June 30, 1993

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<p>This study examined the acute oral and intraperitoneal toxicity of WR242511 tartrate and WR269410 in mice. The dose levels were selected on the basis of range-finding tests. After dosing, the animals were weighed weekly, observed daily for 14 days, and the survivors were necropsied on Day 14. Nonsurvivors were also necropsied.</p> <p>The acute oral LD50s of WR242511 tartrate, administered in 1% methylcellulose/0.4% Tween 80 by gavage, were not significantly different between sexes (males; 23.0 mg base/kg and females; 22.45 mg base/kg). The LD50 values obtained when WR242511 tartrate was administered intraperitoneally in the same vehicle were identical for both sexes (21.82 mg base/kg). Thus, the LD50 of WR242511 tartrate was unaffected by sex or route of administration.</p> <p>Due to dosage formulation problems, WR269410 was administered as a solution in polyethylene glycol 200 (PEG 200). An oral LD50 could not be calculated because of apparent vehicle lethality at the dosing volumes necessary to administer lethal doses of WR269410. The oral LD50 of WR269410 is however estimated to exceed 1000 mg/kg, based on the additive contribution of the vehicle to the mortality observed. In the intraperitoneal acute toxicity test, WR269410 was administered in PEG 200 resulting in a LD50 value of 117.43 mg/kg in males and 190.04 mg/kg in females. Thus, WR269410 is several-fold less acutely toxic than WR242511 tartrate administered by either route. This latter drug also demonstrated a significantly steeper dose-mortality curve.</p>						
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STATEMENT OF COMPLIANCE

To the best of my knowledge, (Study No. 105 - ACUTE ORAL AND INTRAPERITONEAL TOXICITY STUDY OF WR242511 AND WR269410 IN MICE) was conducted in compliance with the Good Laboratory Practices regulations as published in 21 CFR 58, 40 CFR 160 and 40 CFR 792 in all material aspects with the following reservations:

The stability of the test or control articles under the test conditions has not been determined by the testing facility (Sections 105 and 185). This requirement is not applicable since only a single dose was administered in this study. Test article stability will be reported following completion of the repeat dose toxicity studies.

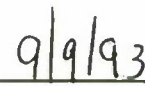
The protocol for this study was approved by the UIC Animal Care Committee.

Signature

Study Director



Barry S. Levine, D.Sc., D.A.B.T.



Date

QUALITY ASSURANCE STATEMENT

STUDY TITLE: ACUTE ORAL AND INTRAPERITONEAL TOXICITY STUDY OF
WR242511 AND WR264910 IN MICE

STUDY NUMBER: 105

STUDY DIRECTOR: BARRY S. LEVINE

INITIATION DATE: 12/3/92

This study has been divided into a series of phases. Using a random sampling approach, Quality Assurance monitors each of these phases over a series of studies. Procedures, equipment, documentation, etc., are examined in order to assure that the study is performed in accordance with the Good Laboratory Practice regulations of the Food and Drug Administration and the Environmental Protection Agency to assure that the study is conducted according to the protocol.

The following are the inspection dates, phases inspected, and report dates of QA inspections of the study.

INSPECT ON 12/7/92, TO STUDY DIR 12/7/92, TO MGMT 12/7/92
PHASES: PROTOCOL REVIEW

INSPECT ON 4/19/93, TO STUDY DIR 4/20/93, TO MGMT 4/22/93
PHASES: ANIMAL RECEIPT AND ROOM ENVIRONMENT

INSPECT ON 4/28/93, TO STUDY DIR 4/29/93, TO MGMT 5/4/93
PHASES: TEST ARTICLE PREPARATION AND ANALYTICAL LABORATORY ANALYSIS

INSPECT ON 4/29/93, TO STUDY DIR 4/29/93, TO MGMT 5/4/93
PHASES: BODY WEIGHT, DOSING (ORAL AND INTRAPERITONEAL) AND CLINICAL SIGNS

INSPECT ON 6/28/93, TO STUDY DIR 6/29/93, TO MGMT 6/29/93
PHASES: RAW DATA AND REPORT FROM ANALYTICAL LABORATORY

INSPECT ON 8/2-3/93, TO STUDY DIR 8/4/93, TO MGMT 8/6/93
PHASES: RAW DATA

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PHASES: DRAFT FINAL REPORT

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9/10/93

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ACUTE ORAL AND INTRAPERITONEAL TOXICITY
STUDY OF WR242511 AND WR269410 IN MICE

TRL Chemical Nos.: 1620614 & 1720614

Sponsor: U.S. Army Medical Materiel
and Development Activity
Frederick, MD 21702-5009

Test Articles: WR242511 Tartrate
WR269410

Sponsor
Representative: George J. Schieferstein, Ph.D.

Testing Facility: Toxicology Research Laboratory (TRL)
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Barry S. Levine, D.Sc., D.A.B.T. 9/9/93
Date

Dosing Initiation: April 29, 1993

In-Life Completion: June 30, 1993

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1. SUMMARY

This study examined the acute oral and intraperitoneal toxicity of WR242511 tartrate and WR269410 in mice. The dose levels were selected on the basis of range-finding tests. After dosing, the animals were weighed weekly, observed daily for 14 days, and the survivors were necropsied on Day 14. Nonsurvivors were also necropsied.

As shown in Table 1, the acute oral LD50s of WR242511 tartrate, administered in 1% methylcellulose/0.4% Tween 80 by gavage, were not significantly different between sexes (males; 23.0 mg base/kg and females; 22.45 mg base/kg). The LD50 values obtained when WR242511 tartrate was administered intraperitoneally in the same vehicle were identical for both sexes (21.82 mg base/kg). Thus, the LD50 of WR242511 tartrate was unaffected by sex or route of administration.

Due to dosage formulation problems, WR269410 was administered as a solution in polyethylene glycol 200 (PEG 200). An oral LD50 could not be calculated because of apparent vehicle lethality at the dosing volumes necessary to administer lethal doses of WR269410. The oral LD50 of WR269410 is however estimated to exceed 1000 mg/kg, based on the additive contribution of the vehicle to the mortality observed. In the intraperitoneal acute toxicity test, WR269410 was administered in PEG 200 resulting in a LD50 value of 117.43 mg/kg in males and 190.04 mg/kg in females (Table 1). Thus, WR269410 is several-fold less acutely toxic than WR242511 tartrate administered by either route. This latter drug also demonstrated a significantly steeper dose-mortality curve.

2. INTRODUCTION

The purpose of this study was to assess the toxicity of the test article in CD¹ mice following a single oral or intraperitoneal dose. The experimental design was based on the Sponsor's requirements. The protocol for this study was approved by the UIC Animal Care Committee. The mouse is a standard and accepted species for toxicology studies, and was specified by the Sponsor. The routes were also specified by the Sponsor. No unforeseen circumstances affected the integrity of the study. Dosing was initiated on April 29, 1993 and the in-life portion was terminated on June 30, 1993.

3. MATERIALS AND METHODS

3.1 Test Articles

The test article (WR242511 Tartrate, Bottle No. BM05816, Lot No. DJD-08-235), a yellow, crystalline powder, was received on December 15, 1992 from Herner & Co. and was assigned an in-house chemical number (1720614). It was stored in the original container at -20 to -15°C and at the ambient relative humidity of the freezer. The Analytical Chemistry Report is contained in Appendix 1. The test article was initially identified by GC-MS and the purity was determined by HPLC ($99.51 \pm 0.02\%$).

The second test article [WR269410 in Polyethylene Glycol 200 (PEG 200); concentration 100 mg/ml] was received on April 27, 1993 from Dr. Douglas R. Flanagan, University of Iowa, College of Pharmacy. The test article was assigned an in-house chemical number (1620614). It was stored in the original container at 0 - 4°C and at the ambient relative humidity of the refrigerator. The Analytical Chemistry Report is contained in Appendix 1. The test article

was initially identified by GC-MS and the purity was determined by HPLC (100%). The concentration of two batches of the received test article in PEG 200 was determined to be 99.95 and 99.5 mg/ml by Dr. Flanagan, and is documented in Appendix 2.

3.2 Dosage Formulations

WR242511 tartrate was administered as a suspension using 1% methylcellulose/0.4% Tween 80 as the vehicle. The dose levels and formulation concentrations of WR242511 tartrate in this report refer to quantities of base, not tartrate salt. Because a suspension of WR269410 in 1% methylcellulose/0.4% Tween 80 could not be passed through needles necessary to dose mice, following discussions with the Sponsor, the drug was administered as a solution in PEG 200. Stock solutions of WR269410 (concentration 100 mg/ml) were received from Dr. Douglas R. Flanagan as described above. Samples of all WR242511 tartrate dosage formulations were analyzed for test article concentration prior to their use. Samples of all WR269410 dosage formulations were sent to Dr. Flanagan for analysis, but the analysis report of test article concentration shown in Appendix 2 was received subsequent to test article use. Therefore, because report analysis was not released prior to dosing, one dosage formulation of WR269410 was used in the acute toxicity study by intraperitoneal administration that was not within 10% of its intended concentration (11.8% of target). The results of these analyses are summarized in Table 2.

3.3 Test System

Virus Antibody Free male and female CD® mice, approximately 6 weeks of age (Date of Birth: March 15, 1993), were obtained from Charles River Breeding Laboratories, Portage, Michigan on April 19, 1993. A second set of Virus Antibody Free male and female CD® mice, approximately 6 weeks of age (Date of Birth: April 27, 1993), were obtained from Charles River Breeding Laboratories, Portage, Michigan on June 09, 1993. Upon arrival, the animals were sexed and examined to determine their health, and were assigned a study-unique quarantine/pretest number. They were individually housed in polycarbonate cages, with Anderson Bed-o-cob® bedding (Heinold Co., Kankakee, IL), which conformed to the upper weight range recommended in the *Guide for the Care and Use of Laboratory Animals*, DHHS (NIH) No. 86.23. Animal room temperature and relative humidity were generally maintained at 65 - 78 °F and 30 - 70%, respectively. The room was on a 14 hour light/10 hour dark cycle. The animals were transferred to clean cages once weekly.

The mice were provided *ad libitum* access to drinking water via an automatic watering system in which the room distribution lines were flushed daily, and to Purina Certified Rodent Chow No. 5002 (Ralston Purina Company, St. Louis MO) except for a 3 - 6 hour fast prior to oral dosing and until \approx 2 hours after dosing. The water was untreated with additional chlorine or HCl. The animals were quarantined for approximately one week prior to test article administration, except for the range-finding test which was conducted during the quarantine period. They were examined by the Clinical Veterinarian near the end of the quarantine period, and were released for placement on test at that time.

3.4 Experimental Design

The study was conducted in phases. The particular phases of the study are designated in the summary and the individual data as follows: (1) the study number, "105" in the first three digits; (2) the route, either "PO" (oral) or "IP" (intraperitoneal) in the next two digits; and (3) the test article, either "24" (WR242511 tartrate) or "26" (WR269410) in the last two digits. One exception exists for this designation of study phase; data obtained from the second group of animals administered WR269410 by gavage. In this case, test article WR269410 is designated by the number "6" and the indication that this is a second set is designated by the letter "A".

In range-finding tests, the selected animals were identified by their pretest number. A cage card appeared on the front of each cage and contained the following information: study number, animal number, test article identification, treatment group number and dose level. Oral dosing (gavage) was accomplished by the use of a rigid oral feeding needle. In intraperitoneal tests, dosing was accomplished by the use of a 25 gauge x 5/8 inch needle.

Body weights were obtained on Day 0 for dosing calculations. The animals were observed for clinical signs and mortality for at least 5 days. Survivors were euthanized and discarded. No post-mortem observations were conducted on these animals.

In acute toxicity tests, at the end of the quarantine/pretest period, 5 animals/sex/group were chosen for the study using a computer generated-randomization program. The selected animals were uniquely identified by an ear tag. A cage card appeared on the front of each cage and contained the following information: study number, animal number, test article identification, treatment group number and dose level.

The test animals were given either a single oral dose or a single intraperitoneal dose of the appropriate concentration of the test article. Following an approximate 3 hour fast, the oral dosing was accomplished by the use of a rigid oral feeding needle. The intraperitoneal dosing was accomplished by the use of a 25 gauge x 5/8 inch needle.

All animals were observed at least three times on Day 0 following test article administration (designated in the data as either "1, 2, or 3", or as "#1, #2 or #3" following the clinical sign of toxicity seen) and daily thereafter. Body weights were obtained in Week -1, and on Days 0, 7 and 14. All test animals which died were grossly necropsied as soon as possible. At fourteen days post-treatment (Day 14), all surviving animals were sacrificed by carbon dioxide and a gross necropsy was performed. The necropsy procedure was a thorough and systematic examination and dissection of the animal viscera and carcass. A veterinary pathologist was available to verify gross lesions. All tissues and organs were discarded following termination of the gross necropsy procedure.

The incidence of all pharmacologic and/or toxicological effects were calculated for each dose levels by sex. For body weights, means and standard deviations were calculated for each dose level by sex and time point. For the toxicity tests, probit analysis of dose-mortality data was

used to calculate the LD50 and its 95% confidence interval and the slope of the dose-mortality curve. The method of Miller and Tainter (1944) was used to calculate an LD50 values because it is able to perform linear regression with one only data point between 0% and 100% mortality, which occurred with WR242511 tartrate due to a very steep dose-mortality curve.

3.4A WR242511 Tartrate

3.4A.1 Range-Finding Test

3.4A.1.1 Gavage

Dose levels listed below were tested in the range-finding test.

<u>Dose Level</u> <u>(mg base/kg)</u>	<u>Dosage</u> <u>Formulation</u> <u>(mg/ml)</u>	<u>Dosing</u> <u>Volume</u> <u>(ml/kg)</u>	<u>No. of</u> <u>Males</u>	<u>No. of</u> <u>Females</u>
15	1.5	10	2	2
20	2.0	10	2	2
25	2.5	10	2	2
35	3.5	10	2	0
50	5.0	10	2	2

3.4A.1.2 Intraperitoneal

Dose levels listed below were tested in the range-finding test.

<u>Dose Level</u> <u>(mg/kg)</u>	<u>Dosage</u> <u>Formulation</u> <u>(mg/ml)</u>	<u>Dosing</u> <u>Volume</u> <u>(ml/kg)</u>	<u>No. of</u> <u>Males</u>	<u>No. of</u> <u>Females</u>
5	1.0	5	0	2
10	2.0	5	0	2
15	3.0	5	2	2
20	4.0	5	2	2
25	5.0	5	2	2
35	7.0	5	2	0
50	10.0	5	2	2

3.4A.2 Acute Toxicity Test

3.4A.2.1 Gavage

Based on the range-finding test, the following were administered.

<u>Treatment Group</u>	<u>Dose Level (mg base/kg)</u>	<u>Dosage Formulation (mg/ml)</u>	<u>Dosing Volume (ml/kg)</u>	<u>No. of Males</u>	<u>No. of Females</u>
1	10	1.0	10	5	5
2	13	1.3	10	5	5
3	17	1.7	10	5	5
4	23	2.3	10	5	5
5	30	3.0	10	5	5

3.4A.2.2 Intraperitoneal

Based on the range-finding test, the following were administered.

<u>Treatment Group</u>	<u>Dose Level (mg base/kg)</u>	<u>Dosage Formulation (mg/ml)</u>	<u>Dosing Volume (ml/kg)</u>	<u>No. of Males</u>	<u>No. of Females</u>
1	10	2.0	5	5	5
2	13	2.6	5	5	5
3	17	3.4	5	5	5
4	23	4.6	5	5	5
5	30	6.0	5	5	5

3.4B WR269410

3.4B.1 Range-Finding Test

3.4B.1.1 Gavage

The following dose levels were tested in the range-finding test.

<u>Dose Level</u> <u>(mg/kg)</u>	<u>Dosage</u> <u>Formulation</u> <u>(mg/ml)</u>	<u>Dosing</u> <u>Volume</u> <u>(ml/kg)</u>	<u>No. of</u> <u>Males</u>	<u>No. of</u> <u>Females</u>
0	0	10	2	2
100	10	10	2	2
400	40	10	2	2
650	65	10	2	2
1000	100	10	2	2
1500	100	15	2	2

3.4B.1.2 Intraperitoneal

The following dose levels were tested in the range-finding test.

<u>Dose Level</u> <u>(mg/kg)</u>	<u>Dosage</u> <u>Formulation</u> <u>(mg/ml)</u>	<u>Dosing</u> <u>Volume</u> <u>(ml/kg)</u>	<u>No. of</u> <u>Males</u>	<u>No. of</u> <u>Females</u>
0	0	5	2	2
100	20	5	2	2
150	30	5	2	2
200	40	5	2	2
400	80	5	2	2

3.4B.2 Acute Toxicity Test

3.4B.2.1 Gavage

Based on the range-finding test, the following were administered. The dosing volume was increased from 10 ml/kg in the range-finding test to 20 ml/kg in order to administer the necessary doses.

<u>Dose</u> <u>Level</u> <u>(mg/kg)</u>	<u>Dosage</u> <u>Formulation</u> <u>(mg/ml)</u>	<u>Dosing</u> <u>Volume</u> <u>(ml/kg)</u>	<u>No. of</u> <u>Males</u>	<u>No. of</u> <u>Females</u>
800	40	20	5	5
1100	55	20	5	5
1300	65	20	5	5
1500	75	20	5	5
1750	87.5	20	5	5
2000	100	20	5	5

A second set of animals was subsequently added to determine if the increase in dosing volume (10 ml/kg in the range-finding tests to 20 ml/kg in the toxicity tests) had contributed to a higher incidence of mortality of WR269410 than expected (see Section 4.2B).

<u>Dose Level (mg/kg)</u>	<u>Dosage Formulation (mg/ml)</u>	<u>Dosing Volume (ml/kg)</u>	<u>No. of Males</u>	<u>No. of Females</u>
0	0	10	5	5
0	0	20	5	5
800	80	10	5	5
1000	100	10	5	5

3.4B.2.2 Intraperitoneal

Based on the range-finding test, the following doses were administered.

<u>Treatment Group</u>	<u>Dose Level (mg/kg)</u>	<u>Dosage Formulation (mg/ml)</u>	<u>Dosing Volume (ml/kg)</u>	<u>No. of Males</u>	<u>No. of Females</u>
1	100	20	5	5	5
2	120	24	5	5	5
3	140	28	5	5	5
4	170	34	5	5	5
5	200	40	5	5	5

4. RESULTS

4.1 Range-Finding Test

4.1A WR242511 Tartrate

4.1A.1 Gavage

4.1A.1.1 Clinical signs

15 mg base/kg: no abnormal signs observed
20 mg base/kg: rough coat, hunched posture, ataxia, found dead
25 mg base/kg: rough coat, hunched posture, found dead
35 mg base/kg: rough coat, hunched posture, found dead (only ♂ dosed)
50 mg base/kg: convulsions, found dead

4.1A.1.2 Mortality

<u>Dose Level (mg base/kg)</u>	<u>Mortality^a</u>	
	<u>Males</u>	<u>Females</u>
15	0/2	0/2
20	2/2	2/2
25	1/2	2/2
35	2/2	-
50	2/2	2/2

^anumber of deaths/number of animals in group.

4.1A.2 Intraperitoneal

4.1A.2.1 Clinical Signs

5 mg base/kg: no abnormal signs observed (♀ only dosed)
10 mg base/kg: no abnormal signs observed (♀ only dosed)
15 mg base/kg: rough coat, hunched posture
20 mg base/kg: rough coat, hunched posture, found dead (♂ only)
25 mg base/kg: rough coat, hunched posture, lethargic, found dead (♀ only)
35 mg base/kg: no abnormal signs observed (♂ only dosed)
50 mg base/kg: rough coat, lethargic, found dead

4.1A.2.2 Mortality

<u>Dose Level (mg base/kg)</u>	<u>Mortality^a</u>	
	<u>Males</u>	<u>Females</u>
5	-	0/2
10	-	0/2
15	0/2	0/2
20	1/2	0/2
25	0/2	2/2
35	0/2	-
50	2/2	2/2

^anumber of deaths/number of animals in group.

4.1B WR269410

4.1B.1 Gavage

4.1B.1.1 Clinical Signs

0 mg/kg: no abnormal signs observed
100 mg/kg: rough coat, decreased activity (slight)
400 mg/kg: rough coat, decreased activity (slight)
650 mg/kg: rough coat, lethargic
1000 mg/kg: rough coat, decreased activity (slight), lethargic
1500 mg/kg: rough coat, decreased activity (slight), lethargic, comatose, found dead

4.1B.1.2 Mortality

<u>Dose Level (mg base/kg)</u>	<u>Mortality^a</u>	
	<u>Males</u>	<u>Females</u>
0	0/2	0/2
100	0/2	0/2
400	0/2	0/2
650	0/2	0/2
1000	0/2	0/2
1500	0/2	1/2

^anumber of deaths/number of animals in group.

4.1B.2 Intraperitoneal

4.1B.2.1 Clinical Signs

0 mg/kg: decreased activity (slight)
100 mg/kg: rough coat, decreased activity (slight), lethargic
150 mg/kg: rough coat, hunched posture, decreased activity (slight), lethargic, comatose, found dead
200 mg/kg: rough coat, decreased activity (slight), lethargic, bloated, ataxia, comatose, found dead
400 mg/kg: found dead

4.1B.2.2 Mortality

Dose Level (mg base/kg)	Mortality ^a	
	Males	Females
0	0/2	0/2
100	0/2	0/2
150	0/2	2/2
200	2/2	2/2
400	2/2	2/2

^anumber of deaths/number of animals in group.

4.2 Acute Toxicity Test

4.2A WR242511 Tartrate

4.2A.1 Gavage

4.2A.1.1 Dosage Formulation Analysis

Dosage formulation analysis is shown in Table 2 and is described with the analytical chemistry methodology in Appendix 1. All test article dosage formulations were within 10% of their intended concentration.

4.2A.1.2 Clinical Signs

Clinical signs of toxicity (hunched posture, decreased activity, lethargy, ataxia) were primarily limited to the two highest treatment groups (23 and 30 mg base/kg) in both sexes. Rough coat was observed in many of the lower dose animals. However, hunched posture was only seen in a few lower dose animals (Tables 3 and 4, and Appendix 3).

4.2A.1.3 Body Weight

Body weights and body weight gains were generally unaffected by test article treatment for those animals which survived the fourteen day observation period (Tables 5, 6, 7 and 8, and Appendix 4).

4.2A.1.4 Necropsy

Necropsy observations are shown in Table 9. Gross lesions were not observed.

4.2A.1.5 Mortality

Dose-mortality data are shown in Table 10 and the LD50 data are shown in Appendix 5. The oral LD50 (and its 95% confidence interval) of WR242511 tartrate for males are 23.0 (15.47 to 34.19) mg base/kg and the dose-mortality curve slope (probit/log dose) is 15.8. For females, the corresponding data are 22.45 (15.14 to 33.29) mg base/kg and the dose-mortality curve slope is 15.9. The LD50 and corresponding values were calculated by the method of Miller and Tainter (1944).

4.2A.2 Intraperitoneal

4.2A.2.1 Dosage Formulation Analysis

Dosage formulation analysis is shown in Table 2 and is described with the analytical chemistry methodology in Appendix 1. All test article dosage formulations were within 10% of their intended concentration.

4.2A.2.2 Clinical Signs

Significant clinical signs of toxicity (hunched posture, decreased activity, ataxia, comatose state) were seen only in the two highest treatment groups (23 and 30 mg base/kg) in both sexes (Tables 3 and 4, and Appendix 3). Rough coat was seen in all treatment groups.

4.2A.2.3 Body Weight

Body weights and body weight gains were generally unaffected by test article treatment for those animals which survived the fourteen day observation period (Tables 5, 6, 7 and 8, and Appendix 4).

4.2A.2.4 Necropsy

Necropsy observations are shown in Table 9. No gross lesions were observed.

4.2A.2.5 Mortality

Dose-mortality data are shown in Table 10 and the LD50 data is shown in Appendix 5. The intraperitoneal LD50 of WR242511 tartrate for both males and females is 21.82 mg base/kg with a 95% confidence interval of 14.75 to 32.29 mg base/kg. The dose-mortality curve slope (probit/ log dose) is 15.99. The LD50 and corresponding values were calculated by the method of Miller and Tainter (1944).

4.2B WR269410

4.2B.1 Gavage (Set 1)

4.2B.1.1 Dosage Formulation Analysis

Dosage formulation analysis is shown in Table 2 and Appendix 2. All test article dosage formulations were within 10% of their intended concentration.

4.2B.1.2 Clinical Signs

Due to the high incidence of mortality, signs of toxicity were observed in all treatment groups in both sexes (Tables 3 and 4, and Appendix 3). Animals which survived generally recovered from treatment-related clinical signs.

4.2B.1.3 Body Weight

Body weights are shown in Tables 5 and 6. All surviving animals gained weight (Tables 7 and 8, and Appendix 4), but because of the high incidence of mortality, differences between treatment groups could not be discerned.

4.2B.1.4 Necropsy

Necropsy observations are shown in Table 9. Gross lesions were not observed.

4.2B.1.5 Mortality

Dose-Mortality data are shown in Table 10. LD50 values could not be calculated due to the excessive mortality seen at all dose levels. See below for further discussion.

4.2B.1 Gavage (Set 2)

A second set of animals were subsequently added to determine if the increase in dosing volume (10 ml/kg in the range-finding tests to 20 ml/kg in the toxicity tests) had contributed to a higher incidence of mortality of WR269410 than expected. This set included two vehicle control groups at different dosing volumes (10 ml/kg and 20 ml/kg), and two test article treatment groups at a dosing volume of 10 ml/kg. The 800 mg/kg dose level was included to allow a comparison to the previous data of 800 mg/kg at a dosing volume of 20 ml/kg.

4.2B.1.1 Dosage Formulation Analysis

Dosage formulation analysis is shown in Table 2 and Appendix 2. The test article dosage formulations were within 10% of their intended concentration.

4.2B.1.2 Clinical Signs

Signs of toxicity (rough coat, hunched posture) were observed in all treatment groups in males, including both vehicle-treated groups (Table 3). Decreased activity was seen in vehicle-treated (dosing volume of 10 ml/kg) and WR269410-treated (1000 mg/kg) males. In vehicle-treated females administered 10 ml/kg, only rough coats were observed. All other female treatment groups, including vehicle-treated at a dosing volume of 20 ml/kg, demonstrated rough coat, hunched posture, decreased activity, and lethargy following treatment. Blue feet were seen in WR269410-treated females at a dose of 1000 mg/kg.

4.2B.1.3 Body Weight

Body weights and weight gains are shown in Tables 5, 6, 7 and 8, and Appendix 4. A significant decrease in weight gain was observed in test article-treated males as compared to vehicle-treated males. In female mice, 1000 mg/kg treated females lost body weight. All other treatment groups of both sexes gained a minimal amount of weight in the 14-day observation period.

4.2B.1.4 Necropsy

Necropsy observations are shown in Table 9. A subcutaneous cyst was seen in one 0 mg/kg (10 ml/kg) male and one 800 mg/kg WR269410-treated male. An enlarged mesenteric lymph node was seen in a vehicle-treated male (10 ml/kg). Also, a 1000 mg/kg WR269410-treated female had an irregular shaped lesion on the left kidney (~ 0.6 cm band around the midzone).

4.2B.1.5 Mortality

Dose-mortality data is shown in Table 10 and LD50 data is shown in Appendix 5. PEG 200 toxicity is evident in both vehicle treated groups, except for females receiving a dosing volume of 10 ml/kg. Accordingly, an oral LD50 could not be calculated from the dose-mortality data obtained in both sets. However, cursory inspection of all data including vehicle mortality suggests that the oral LD50 of WR269410 is greater than 1000 mg/kg.

4.2B.2 Intraperitoneal

4.2B.2.1 Dosage Formulation Analysis

Dosage formulation analysis is shown in Table 2 and Appendix 2. All test article dosage formulations were within 10% of their intended concentration, except for the mid dose treatment group. The dosage formulation of 28 mg/ml, the 140 mg/kg treated animals, was administered in 11.8 % excess of its intended concentration because report analysis was not released prior to dosing.

4.2B.2.2 Clinical Signs

Signs of toxicity (rough coat, hunched posture, decreased activity, lethargy) were observed in all treatment groups; characterized by an increase of incidence with ascending dose levels (Tables 3 and 4, Appendix 3).

4.2B.2.3 Body Weight

Body weights and body weight gains were generally unaffected by test article treatment for those animals which survived the fourteen day observation period (Tables 5, 6, 7 and 8, and Appendix 4).

4.2B.2.4 Necropsy

Necropsy observations are shown in Table 9. One female treated with 140 mg/kg WR269410 had a fusion of the lobes of liver with the diaphragm. One male treated with 170 mg/kg of WR269410 had apparent fusion of the lobes of the liver.

4.2B.2.5 Mortality

The dose-mortality data is shown in Table 10 and the LD50 data is shown in Appendix 5. The intraperitoneal LD50 of WR269410 for male mice is 117.43 mg/kg with a 95% confidence interval of 89.56 to 153.97 mg/kg and the dose-mortality curve slope is 7.47. For female mice, the calculated intraperitoneal LD50 is 190.04 mg/kg with a 95% confidence interval of 134.87 to 267.78 mg/kg. The dose-mortality curve slope is 7.80. The method of Miller and Tainter (1944) was used to calculate LD50 values.

5.0 DISCUSSION/CONCLUSION

In the oral acute toxicity test of WR242511 tartrate, the test article was administered in 1% methylcellulose/0.4% Tween 80 by gavage to five groups of mice (5 animals/sex) at single oral doses of 10, 13, 17, 23 and 30 mg base/kg. LD50s of WR242511 tartrate were calculated using the method of Miller and Tainter (1944), and are shown in Table 1. The oral LD50 of WR242511 tartrate for male

mice is 23.0 mg base/kg with a 95% confidence interval of 15.47 to 34.19 mg base/kg and the dose-mortality curve slope (probit/log dose) is 15.8. The calculated LD50 for female mice is 22.45 mg base/kg with a 95% confidence interval of 15.14 to 33.29 mg base/kg and the dose-mortality curve slope is 15.9. In the intraperitoneal acute toxicity test of WR242511 tartrate, the test article was administered in 1% methylcellulose/0.4% Tween 80 to five groups of mice (5 animals/sex) at single doses of 10, 13, 17, 23 and 30 mg base/kg. From the results of the toxicity test, the calculated intraperitoneal LD50 of WR242511 tartrate for both male and female mice is 21.82 mg base/kg with a 95% confidence interval of 14.75 to 32.29 mg base/kg. The dose-mortality curve slope (probit/ log dose) is 15.99. Because of the similarity of the LD50 values, 95% confidence intervals, and dose-mortality curve slopes, these data demonstrate that the LD50 value of WR242511 tartrate is unaffected by either sex or route of administration. This is an unexpected finding: one would expect the oral route to yield a lower LD50 value because the drug must first undergo reduction to yield the physiologically active compound responsible for the formation of methemoglobin.

Due to dosage formulation problems, WR269410 was administered as a solution in polyethylene glycol 200 (PEG 200) received from Dr. Douglas R. Flanagan of the University of Iowa. An oral LD50 for WR269410 could not be calculated because of excessive mortality at all dose levels tested and the apparent lack of a dose-response relationship. A second set of animals was added to determine if this was caused by the increase in the dosing volume from 10 ml/kg (most of the range-finding tests) to 20 ml/kg in the acute toxicity tests. This increase was necessary to administer sufficiently high and therefore lethal doses. The second set of data demonstrated that the vehicle alone contributed to the mortality and clinical signs of toxicity observed in mice. Therefore, this vehicle was inappropriate for oral administration in mice. Although, an oral LD50 of the test article could not be calculated from these data, it can be estimated assuming that PEG 200 contributed additively to the lethality observed. If the data from both sexes are combined at each dose level, it is estimated that the oral LD50 exceeds 1000 mg/kg for acute administration of the test article.

In the intraperitoneal acute toxicity test, WR269410 was administered in PEG 200 to five groups of mice (5 animals/sex) at single doses of 100, 120, 140 170 and 200 mg/kg. LD50s of WR269410 were calculated using the method of Miller and Tainter (1944). The calculated intraperitoneal LD50 of WR269410 for male mice is 117.43 mg/kg with a 95% confidence interval of 89.56 to 153.97 mg/kg and the dose-mortality curve slope is 7.47 (Table 1). For female mice, the calculated intraperitoneal LD50 is 190.04 mg/kg with a 95% confidence interval of 134.87 to 267.78 mg/kg. The dose-mortality curve slope is 7.80. Thus, female mice are slightly less susceptible to WR269410-induced toxicity than male mice. Also, based on the estimated oral and the calculated intraperitoneal LD50 values of WR269410, this drug is several-fold less acutely toxic than WR242511 tartrate administered by either route in both sexes. WR242511 tartrate also demonstrated a significantly steeper dose-mortality curve.

6.0 PERSONNEL:

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7.0 ARCHIVES

The raw data, test article reserve sample and final report are archived at the Toxicology Research Laboratory (TRL), University of Illinois at Chicago (UIC), Department of Pharmacology, 1940 W. Taylor St., Chicago, IL 60612-7353.

8.0 REFERENCE

Miller and Tainter (1944). Estimation of the LD50 and its error by means of logarithmic-probit graph paper. *Proc. Soc. Exp. Bio Med.* 57, 261-264.

Table 1

**ACUTE ORAL AND INTRAPERITONEAL TOXICITY
STUDY OF WR242511 AND WR269410 IN MICE**

Calculated LD50 Values

WR242511 Tartrate

Route	Sex	LD50 (mg base/kg)	95% Confidence Interval (mg base/kg)	Dose-Mortality Curve Slope (probit/log dose)
Oral	Male	23.00	15.47 - 34.19	15.80
	Female	22.45	15.14 - 33.29	15.90
Intraperitoneal	Male	21.82	14.75 - 32.29	15.99
	Female	21.82	14.75 - 32.29	15.99

WR269410

Route	Sex	LD50 (mg/kg)	95% Confidence Interval (mg/kg)	Dose-Mortality Curve Slope (probit/log dose)
Intraperitoneal	Male	117.43	89.56 - 153.97	7.47
	Female	190.04	134.87 - 267.78	7.80

Table 2

ACUTE ORAL AND INTRAPERITONEAL TOXICITY
STUDY OF WR242511 AND WR269410 IN MICE

Dosage Formulation Analysis^a

WR242511 Tartrate (Gavage)

Target Concentration (mg/ml)	Day 0 ^b	% Target
1.0	0.99 ± 0.0133	98.9
1.3	1.31 ± 0.0070	100.5
1.7	1.69 ± 0.0297	99.6
2.3	2.32 ± 0.0437	101.0
3.0	2.97 ± 0.0061	99.1

WR242511 Tartrate (Intraperitoneal)

Target Concentration (mg/ml)	Day 0 ^b	% Target
2.0	2.17 ± 0.0096	108.7
2.6	2.55 ± 0.0203	98.0
3.4	3.39 ± 0.0411	99.8
4.6	4.58 ± 0.0336	99.7
6.0	5.81 ± 0.0037	96.9

^aMean ± standard deviation for triplicate runs.

^bThe samples were assayed within 24 hours prior to use.

Table 2 (contd.)

ACUTE ORAL AND INTRAPERITONEAL TOXICITY
STUDY OF WR242511 AND WR269410 IN MICE

Dosage Formulation Analysis^a

WR269410 (Gavage) Set 1

Target Concentration (mg/ml)	Day 0 ^b	% Target
40	40.3	100.8
55	50.3	91.5
65	66.8	102.8
75	77.6	103.5
87.5	84.2	96.3
100	100.0	100.0

WR269410 (Gavage) Set 2

Target Concentration (mg/ml)	Day 0 ^b	% Target
80	73.2	91.5
100	100.0	100.0

WR269410 (Intraperitoneal)

Target Concentration (mg/ml)	Day 0 ^b	% Target
20	18.2	91.0
24	26.4	110.0
28	31.3	111.8
34	31.7	93.2
40	40.3	100.8

^aMean \pm standard deviation for triplicate runs.

^bThe samples were assayed within 24 hours prior to use.

Table 3.1

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

SUMMARY OF CLINICAL SIGNS

STUDY: 105PO24

SEX: MALE

DOSE:(mg/kg) GROUP:	10 1-M	13 2-M	17 3-M	23 4-M	30 5-M
Scheduled Sacrifice	5	5	5	3	0
Animal Found Dead	0	0	0	2	5
Activity Decreased	0	0	0	2	0
Ataxia	0	0	0	1	0
Comatose	0	0	0	0	1
Hunched Posture	0	0	0	1	0
Lethargic	0	0	0	1	1
Rough Coat	2	3	4	4	3
Total Number of Animals	5	5	5	5	5

Table 3.2

**ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE**

SUMMARY OF CLINICAL SIGNS

STUDY: 105IP24

SEX: MALE

DOSE:(mg/kg) GROUP:	10 1-M	13 2-M	17 3-M	23 4-M	30 5-M
Scheduled Sacrifice	5	5	5	1	0
Animal Found Dead	0	0	0	4	5
Activity Decreased	0	0	0	1	4
Ataxia	0	0	0	0	2
Hunched Posture	0	0	0	2	1
Rough Coat	5	5	5	5	4
Total Number of Animals	5	5	5	5	5

Table 3.3

**ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE**

SUMMARY OF CLINICAL SIGNS

STUDY: 105PO26

SEX: MALE

DOSE:(mg/kg) GROUP:	1100 1-M	1300 2-M	1500 3-M	1750 4-M	2000 5-M	800 6-M
Scheduled Sacrifice	3	2	1	0	1	1
Animal Found Dead	2	3	4	5	4	4
Activity Decreased	0	1	0	0	1	1
Comatose	0	0	0	0	1	0
Hunched Posture	0	1	1	0	1	0
Lethargic	0	0	0	0	1	1
Rough Coat	3	2	1	0	2	2
Lethargic #1	1	2	1	1	1	3
Lethargic #2	0	1	2	2	2	3
Lethargic #3	0	1	2	3	1	2
Activity Decreased #1	4	3	3	3	1	2
Activity Decreased #2	4	2	1	2	1	2
Activity Decreased #3	4	2	2	1	2	3
Comatose #1	0	0	1	1	2	0
Comatose #2	1	1	2	1	2	0
Comatose #3	1	1	1	1	2	0
Rough Coat #1	1	1	1	0	1	2
Rough Coat #2	1	3	1	0	1	2
Rough Coat #3	4	3	1	0	2	3
Total Number of Animals	5	5	5	5	5	5

Table 3.4

**ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE**

SUMMARY OF CLINICAL SIGNS

STUDY: 105PO6A

SEX: MALE

DOSE:(mg/kg) GROUP:	0 1-M	0 2-M	800 3-M	1000 4-M
Scheduled Sacrifice	4	4	2	4
Animal Found Dead	1	1	3	1
Decreased Activity	1	0	0	1
Hunched Posture	1	2	1	4
Rough Coat	5	4	2	4
Rough Coat 1	1	4	3	4
Rough Coat 2	1	4	4	4
Rough Coat 3	1	4	4	4
Hunched Posture 1	0	1	0	4
Hunched Posture 2	0	0	0	3
Hunched Posture 3	0	0	0	2
Decreased Activity 1	1	0	2	2
Decreased Activity 2	1	0	3	1
Decreased Activity 3	1	0	2	2
Total Number of Animals	5	5	5	5

Table 3.5

**ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE**

SUMMARY OF CLINICAL SIGNS

STUDY: 105IP26

SEX: MALE

DOSE:(mg/kg) GROUP:	100 1-M	120 2-M	140 3-M	170 4-M	200 5-M
Scheduled Sacrifice	4	1	2	1	0
Animal Found Dead	1	4	3	4	5
Activity Decreased	0	4	2	3	2
Ataxia	0	0	0	2	0
Comatose	0	1	0	0	0
Hunched Posture	0	2	1	3	1
Rough Coat	5	4	5	4	2
Rough Coat #1	4	0	0	0	0
Comatose #1	0	3	4	5	5
Activity Decreased #2	5	3	1	0	0
Rough Coat #2	5	1	1	0	0
Comatose #2	0	0	1	3	5
Activity Decreased #3	4	4	1	1	0
Comatose #3	0	0	1	1	3
Rough Coat #3	5	4	1	1	0
Lethargic #1	1	2	1	0	0
Lethargic #2	0	2	3	2	0
Lethargic #3	0	1	3	3	2
Activity Decreased #1	4	0	0	0	0
Total Number of Animals	5	5	5	5	5

Table 4.1

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

SUMMARY OF CLINICAL SIGNS

STUDY: 105PO24

SEX: FEMALE

DOSE:(mg/kg) GROUP:	10 1-F	13 2-F	17 3-F	23 4-F	30 5-F
Scheduled Sacrifice	5	5	5	2	0
Animal Found Dead	0	0	0	3	5
Ataxia	0	0	0	1	2
Dehydrated	0	0	1	0	0
Hunched Posture	0	0	1	1	0
Lethargic	0	0	0	0	2
Rough Coat	0	1	2	2	0
Total Number of Animals	5	5	5	5	5

Table 4.2

**ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE**

SUMMARY OF CLINICAL SIGNS

STUDY: 105IP24

SEX: FEMALE

DOSE:(mg/kg) GROUP:	10 1-F	13 2-F	17 3-F	23 4-F	30 5-F
Scheduled Sacrifice	5	5	5	1	0
Animal Found Dead	0	0	0	4	5
Activity Decreased	0	0	0	3	2
Ataxia	0	0	0	1	1
Comatose	0	0	0	0	1
Hunched Posture	0	0	0	1	0
Rough Coat	2	2	5	4	5
Total Number of Animals	5	5	5	5	5

Table 4.3
ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

SUMMARY OF CLINICAL SIGNS						
STUDY: 105PO26		SEX: FEMALE				
DOSE:(mg/kg) GROUP:	1100 1-F	1300 2-F	1500 3-F	1750 4-F	2000 5-F	800 6-F
Scheduled Sacrifice	1	1	1	0	0	0
Animal Found Dead	4	4	4	5	5	5
Activity Decreased	0	0	1	0	0	0
Comatose	0	0	0	0	0	1
Hunched Posture	1	1	1	0	0	0
Lethargic	1	0	1	1	0	0
Rough Coat	2	1	2	1	1	2
Lethargic #1	2	2	3	0	3	4
Lethargic #2	1	1	1	1	0	3
Lethargic #3	2	1	1	2	1	2
Activity Decreased #1	2	3	1	2	2	1
Activity Decreased #2	1	3	3	1	1	2
Activity Decreased #3	1	2	2	1	2	3
Comatose #1	1	0	1	3	0	0
Comatose #2	2	1	1	3	4	0
Comatose #3	1	1	1	2	1	0
Rough Coat #1	1	3	0	1	0	1
Rough Coat #2	2	3	3	1	1	2
Rough Coat #3	2	2	3	2	2	3
Hunched Posture #3	0	2	0	0	0	0
Total Number of Animals	5	5	5	5	5	5

Table 4.4

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

SUMMARY OF CLINICAL SIGNS				
STUDY: 105PO6A		SEX: FEMALE		
DOSE:(mg/kg) GROUP:	0 1-F	0 2-F	800 3-F	1000 4-F
Scheduled Sacrifice	5	3	3	3
Animal Found Dead	0	2	2	2
Hunched Posture	0	0	3	3
Rough Coat	3	2	3	3
Rough Coat 1	0	5	4	4
Rough Coat 2	0	5	5	4
Rough Coat 3	0	5	5	4
Hunched Posture 1	0	4	0	3
Hunched Posture 2	0	2	1	4
Hunched Posture 3	0	2	1	4
Blue Feet 1	0	0	0	3
Blue Feet 2	0	0	0	1
Decreased Activity 1	0	4	3	3
Decreased Activity 2	0	2	2	2
Decreased Activity 3	0	1	2	2
Lethargic 1	0	0	1	0
Lethargic 2	0	0	1	0
Lethargic 3	0	1	1	0
Labored Breathing 2	0	0	1	0
Labored Breathing 3	0	0	1	0
Total Number of Animals	5	5	5	5

Table 4.5

**ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE**

SUMMARY OF CLINICAL SIGNS

STUDY: 105IP26

SEX: FEMALE

DOSE:(mg/kg) GROUP:	100 1-F	120 2-F	140 3-F	170 4-F	200 5-F
Scheduled Sacrifice	5	5	3	4	2
Animal Found Dead	0	0	2	1	3
Activity Decreased	0	0	1	0	0
Hunched Posture	0	1	0	0	3
Lethargic	0	0	1	2	0
Rough Coat	5	5	5	5	3
Rough Coat #1	1	1	0	0	0
Comatose #1	0	2	4	5	5
Activity Decreased #2	5	1	0	0	0
Rough Coat #2	1	1	2	0	0
Comatose #2	0	1	1	5	2
Activity Decreased #3	5	3	1	1	0
Comatose #3	0	0	0	1	2
Rough Coat #3	5	5	2	3	0
Lethargic #1	1	1	1	0	0
Lethargic #2	0	3	4	0	1
Lethargic #3	0	2	4	3	1
Activity Decreased #1	4	2	0	0	0
Total Number of Animals	5	5	5	5	5

Table 5.1

**ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE**

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: 105PO24

SEX: MALE

PERIOD	DOSE: (mg/kg) GROUP:	10 1-M	13 2-M	17 3-M	23 4-M	30 5-M
DAY -3	MEAN	25.9	26.0	26.1	25.9	26.0
	S.D.	1.12	1.66	1.14	1.37	1.43
	N	5	5	5	5	5
DAY 0	MEAN	27.2	27.7	27.3	27.0	27.7
	S.D.	0.83	1.66	1.53	1.23	2.03
	N	5	5	5	5	5
DAY 7	MEAN	28.7	29.9	28.8	30.3	--
	S.D.	0.61	1.31	2.16	0.51	--
	N	5	5	5	3	0
DAY 14	MEAN	30.6	31.8	30.6	32.5	--
	S.D.	1.05	1.99	2.43	1.01	--
	N	5	5	5	3	0

* P less than .05
** P less than .01

Analysis of Variance using DUNNETT'S Procedure

Table 5.2

**ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE**

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: 105IP24

SEX: MALE

PERIOD	DOSE: (mg/kg) GROUP:	10 1-M	13 2-M	17 3-M	23 4-M	30 5-M
DAY -3	MEAN	25.9	26.2	26.2	26.0	26.1
	S.D.	1.53	1.55	1.45	1.55	1.48
	N	5	5	5	5	5
DAY 0	MEAN	27.6	27.4	28.2	27.4	27.4
	S.D.	1.98	1.38	1.11	1.99	0.99
	N	5	5	5	5	5
DAY 7	MEAN	28.6	29.0	29.0	27.0	--
	S.D.	1.79	2.03	0.23	0.00	--
	N	5	5	5	1	0
DAY 14	MEAN	31.0	30.8	31.7	29.6	--
	S.D.	2.55	2.43	0.76	0.00	--
	N	5	5	5	1	0

* P less than .05

** P less than .01

Analysis of Variance using DUNNETT'S Procedure

Table 5.3

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: 105PO26

SEX: MALE

PERIOD	DOSE: (mg/kg) GROUP:	1100 1-M	1300 2-M	1500 3-M	1750 4-M	2000 5-M	800 6-M
PRETEST	MEAN	28.3	28.3	28.3	28.1	28.3	25.8
	S.D.	1.55	2.20	1.46	2.31	1.65	1.84
	N	5	5	5	5	5	5
DAY 0	MEAN	29.4	29.3	29.6	29.1	29.5	27.7
	S.D.	1.24	2.61	1.59	2.37	1.72	2.65
	N	5	5	5	5	5	5
DAY 7	MEAN	29.8	27.5	25.9	--	26.6	26.6
	S.D.	1.07	4.45	0.00	--	0.00	0.00
	N	3	2	1	0	1	1
DAY 14	MEAN	30.6	31.2	30.8	--	29.2	27.6
	S.D.	1.37	0.28	0.00	--	0.00	0.00
	N	3	2	1	0	1	1

* P less than .05

** P less than .01

Analysis of Variance using DUNNETT'S Procedure

Table 5.4
ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: 105PO6A

SEX: MALE

PERIOD	DOSE: (mg/kg) GROUP:	0 1-M	0 2-M	800 3-M	1000 4-M
DAY -2	MEAN	28.6	29.0	28.5	28.3
	S.D.	1.32	1.33	1.68	1.61
	N	5	5	5	5
DAY 0	MEAN	28.7	29.9	29.4	29.2
	S.D.	1.06	1.37	1.72	1.61
	N	5	5	5	5
DAY 7	MEAN	32.4	32.4	30.2	31.4
	S.D.	0.88	1.46	2.90	2.11
	N	4	4	2	4
DAY 14	MEAN	29.7	32.7	29.5	31.5
	S.D.	4.50	1.01	2.12	1.74
	N	4	4	2	4

* P less than .05
** P less than .01

Analysis of Variance using DUNNETT'S Procedure

Table 5.5

**ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE**

SUMMARY OF BODY WEIGHTS (Grams)						
STUDY: 105IP26			SEX: MALE			
PERIOD	DOSE: (mg/kg) GROUP:	100 1-M	120 2-M	140 3-M	170 4-M	200 5-M
DAY -3	MEAN	28.1	28.3	28.1	28.3	28.4
	S.D.	1.33	1.42	2.09	1.03	1.82
	N	5	5	5	5	5
DAY 0	MEAN	29.3	29.4	29.0	29.4	29.0
	S.D.	0.90	1.50	1.89	1.09	1.58
	N	5	5	5	5	5
DAY 7	MEAN	29.1	31.7	31.7	25.9	--
	S.D.	1.98	0.00	0.99	7.42	--
	N	4	1	2	2	0
DAY 14	MEAN	29.9	33.3	33.3	32.0	--
	S.D.	3.62	0.00	0.07	0.00	--
	N	4	1	2	1	0

* P less than .05

** P less than .01

Analysis of Variance using DUNNETT'S Procedure

Table 6.1
ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

SUMMARY OF BODY WEIGHTS (Grams)						
STUDY: 105PO24			SEX: FEMALE			
PERIOD	DOSE: (mg/kg) GROUP:	10 1-F	13 2-F	17 3-F	23 4-F	30 5-F
DAY -3	MEAN	22.8	23.0	23.3	23.2	23.2
	S.D.	1.36	1.26	1.22	1.62	1.17
	N	5	5	5	5	5
DAY 0	MEAN	23.8	24.0	23.9	23.1	23.8
	S.D.	1.28	1.85	1.33	1.31	1.00
	N	5	5	5	5	5
DAY 7	MEAN	25.3	25.4	23.8	23.0	--
	S.D.	1.18	1.56	3.37	1.27	--
	N	5	5	5	2	0
DAY 14	MEAN	26.4	26.9	27.8	25.0	--
	S.D.	1.80	2.01	2.05	0.71	--
	N	5	5	5	2	0

* P less than .05
** P less than .01
-- = Data Unavailable

Analysis of Variance using DUNNETT'S Procedure

Table 6.2

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: 105IP24

SEX: FEMALE

PERIOD	DOSE: (mg/kg) GROUP:	10 1-F	13 2-F	17 3-F	23 4-F	30 5-F
DAY -3	MEAN	23.0	23.2	23.3	23.1	23.1
	S.D.	1.35	1.12	1.39	1.06	1.94
	N	5	5	5	5	5
DAY 0	MEAN	24.3	24.4	24.8	24.4	24.2
	S.D.	1.05	1.13	1.31	1.37	1.97
	N	5	5	5	5	5
DAY 7	MEAN	25.9	25.3	25.3	25.8	--
	S.D.	2.22	0.74	1.83	0.00	--
	N	5	5	5	1	0
DAY 14	MEAN	26.9	27.5	27.3	26.5	--
	S.D.	1.47	0.98	2.14	0.00	--
	N	5	5	5	1	0

* P less than .05
 ** P less than .01
 -- = Data Unavailable

Analysis of Variance using DUNNETT'S Procedure

Table 6.3
ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

SUMMARY OF BODY WEIGHTS (Grams)							
STUDY: 105PO26				SEX: FEMALE			
PERIOD	DOSE: (mg/kg) GROUP:	1100 1-F	1300 2-F	1500 3-F	1750 4-F	2000 5-F	800 6-F
PRETEST	MEAN	24.6	25.2	24.7	24.8	24.6	22.6
	S.D.	1.54	1.77	1.24	1.33	1.70	2.89
	N	5	5	5	5	5	5
DAY 0	MEAN	24.7	25.1	24.8	25.4	24.8	23.6
	S.D.	1.86	2.01	0.50	1.13	2.22	1.74
	N	5	5	5	5	5	5
DAY 7	MEAN	25.3	19.5	19.8	--	--	--
	S.D.	0.00	0.00	0.00	--	--	--
	N	1	1	1	0	0	0
DAY 14	MEAN	26.9	25.0	26.4	--	--	--
	S.D.	0.00	0.00	0.00	--	--	--
	N	1	1	1	0	0	0

* P less than .05
** P less than .01
-- = Data Unavailable

Analysis of Variance using DUNNETT'S Procedure

Table 6.4

**ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE**

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: 105PO6A

SEX: FEMALE

PERIOD	DOSE: (mg/kg) GROUP:	0 1-F	0 2-F	800 3-F	1000 4-F
DAY -2	MEAN	23.4	23.5	23.2	23.2
	S.D.	1.24	1.06	1.33	1.62
	N	5	5	5	5
DAY 0	MEAN	23.7	23.9	24.1	24.2
	S.D.	0.61	1.03	0.93	1.20
	N	5	5	5	5
DAY 7	MEAN	26.0	24.4	26.3	23.6
	S.D.	1.32	0.81	1.94	2.80
	N	5	3	3	3
DAY 14	MEAN	24.3	25.6	26.9	22.4
	S.D.	4.36	1.78	0.93	5.66
	N	5	3	3	3

* P less than .05

** P less than .01

Analysis of Variance using DUNNETT'S Procedure

Table 6.5

**ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE**

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: 105IP26

SEX: FEMALE

PERIOD	DOSE: (mg/kg) GROUP:	100 1-F	120 2-F	140 3-F	170 4-F	200 5-F
DAY -3	MEAN	24.6	24.8	25.0	24.9	24.6
	S.D.	1.51	1.16	1.48	1.66	1.46
	N	5	5	5	5	5
DAY 0	MEAN	24.9	24.7	25.5	25.1	25.0
	S.D.	1.56	1.66	1.57	2.06	2.06
	N	5	5	5	5	5
DAY 7	MEAN	25.8	26.0	26.9	26.9	27.1
	S.D.	1.64	1.92	1.32	1.19	0.92
	N	5	5	3	4	2
DAY 14	MEAN	26.3	26.6	28.2	27.6	29.2
	S.D.	1.50	1.22	0.65	1.59	0.35
	N	5	5	3	4	2

* P less than .05
 ** P less than .01

Analysis of Variance using DUNNETT'S Procedure

Table 7.1

**ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE**

SUMMARY OF WEIGHT GAINS (Grams)						
STUDY: 105PO24			SEX: MALE			
PERIOD	DOSE: (mg/kg) GROUP:	10 1-M	13 2-M	17 3-M	23 4-M	30 5-M
DAY 7	MEAN	1.5	2.2	1.5	3.0*	--
	S.D.	0.64	0.68	1.11	0.10	--
	N	5	5	5	3	0
DAY 14	MEAN	1.8	1.9	1.8	2.2	--
	S.D.	0.73	1.06	0.48	1.04	--
	N	5	5	5	3	0
TOTAL GAIN	MEAN	3.3	4.1	3.3	5.2	--
	S.D.	1.04	1.38	1.26	1.06	--
	N	5	5	5	3	0

* P less than .05
 ** P less than .01

Analysis of Variance using DUNNETT'S Procedure

Table 7.2

**ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE**

SUMMARY OF WEIGHT GAINS (Grams)						
STUDY: 105IP24			SEX: MALE			
PERIOD	DOSE: (mg/kg) GROUP:	10 1-M	13 2-M	17 3-M	23 4-M	30 5-M
DAY 7	MEAN	0.9	1.6	0.8	-0.2	--
	S.D.	0.34	0.65	1.26	0.00	--
	N	5	5	5	1	0
DAY 14	MEAN	2.5	1.8	2.6	2.6	--
	S.D.	1.21	0.64	0.80	0.00	--
	N	5	5	5	1	0
TOTAL GAIN	MEAN	3.4	3.4	3.5	2.4	--
	S.D.	1.40	1.11	0.82	0.00	--
	N	5	5	5	1	0

* P less than .05
** P less than .01

Analysis of Variance using DUNNETT'S Procedure

Table 7.3

**ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE**

SUMMARY OF WEIGHT GAINS (Grams)							
STUDY: 105P026				SEX: MALE			
PERIOD	DOSE: (mg/kg) GROUP:	1100 1-M	1300 2-M	1500 3-M	1750 4-M	2000 5-M	800 6-M
DAY 7	MEAN	1.0	-2.1	-2.7	--	-2.2	0.9
	S.D.	0.10	5.73	0.00	--	0.00	0.00
	N	3	2	1	0	1	1
DAY 14	MEAN	0.8	3.8	4.9	--	2.6	1.0
	S.D.	0.31	4.74	0.00	--	0.00	0.00
	N	3	2	1	0	1	1
TOTAL GAIN	MEAN	1.8	1.7	2.2	--	0.4	1.9
	S.D.	0.25	0.99	0.00	--	0.00	0.00
	N	3	2	1	0	1	1

* P less than .05
 ** P less than .01
 -- = Data Unavailable

Analysis of Variance using DUNNETT'S Procedure

Table 7.4

**ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE**

SUMMARY OF WEIGHT GAINS (Grams)					
STUDY: 105PO6A			SEX: MALE		
PERIOD	DOSE: (mg/kg) GROUP:	0 1-M	0 2-M	800 3-M	1000 4-M
DAY 7	MEAN	4.1	2.9	1.9*	2.3*
	S.D.	1.14	0.51	0.92	0.40
	N	4	4	2	4
DAY 14	MEAN	-2.7	0.3	-0.7	0.1
	S.D.	5.27	0.87	0.78	0.87
	N	4	4	2	4
TOTAL GAIN	MEAN	1.4	3.2	1.2	2.4
	S.D.	4.37	0.53	0.14	0.53
	N	4	4	2	4

* P less than .05
 ** P less than .01

Analysis of Variance using DUNNETT'S Procedure

Table 7.5

**ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE**

SUMMARY OF WEIGHT GAINS (Grams)						
STUDY: 105IP26			SEX: MALE			
PERIOD	DOSE: (mg/kg) GROUP:	100 1-M	120 2-M	140 3-M	170 4-M	200 5-M
DAY 7	MEAN	0.1	0.2	1.0	-3.5	--
	S.D.	1.30	0.00	0.14	6.01	--
	N	4	1	2	2	0
DAY 14	MEAN	0.8	1.6	1.6	0.9	--
	S.D.	2.18	0.00	1.06	0.00	--
	N	4	1	2	1	0
TOTAL GAIN	MEAN	0.9	1.8	2.6	1.7	--
	S.D.	2.92	0.00	1.20	0.00	--
	N	4	1	2	1	0

* P less than .05
 ** P less than .01

Analysis of Variance using DUNNETT'S Procedure

Table 8.1

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

SUMMARY OF WEIGHT GAINS (Grams)						
STUDY: 105PO24			SEX: FEMALE			
PERIOD	DOSE: (mg/kg) GROUP:	10 1-F	13 2-F	17 3-F	23 4-F	30 5-F
DAY 7	MEAN	1.6	1.4	-0.1	0.1	--
	S.D.	0.83	1.57	3.24	2.12	--
	N	5	5	5	2	0
DAY 14	MEAN	1.1	1.5	4.0	2.0	--
	S.D.	1.31	0.91	4.04	0.57	--
	N	5	5	5	2	0
TOTAL GAIN	MEAN	2.6	2.9	3.9	2.1	--
	S.D.	0.62	2.04	1.12	1.56	--
	N	5	5	5	2	0

* P less than .05
 ** P less than .01
 -- = Data Unavailable

Analysis of Variance using DUNNETT'S Procedure

Table 8.2

**ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE**

SUMMARY OF WEIGHT GAINS (Grams)						
STUDY: 105IP24			SEX: FEMALE			
PERIOD	DOSE: (mg/kg) GROUP:	10 1-F	13 2-F	17 3-F	23 4-F	30 5-F
DAY 7	MEAN	1.6	0.9	0.5	1.6	--
	S.D.	1.67	0.50	0.57	0.00	--
	N	5	5	5	1	0
DAY 14	MEAN	1.0	2.2	2.0	0.7	--
	S.D.	1.37	1.06	0.69	0.00	--
	N	5	5	5	1	0
TOTAL GAIN	MEAN	2.6	3.1	2.5	2.3	--
	S.D.	1.49	1.00	1.08	0.00	--
	N	5	5	5	1	0

* P less than .05
 ** P less than .01
 -- = Data Unavailable

Analysis of Variance using DUNNETT'S Procedure

Table 8.3

**ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE**

SUMMARY OF WEIGHT GAINS (Grams)

STUDY: 105PO26

SEX: FEMALE

PERIOD	DOSE: (mg/kg) GROUP:	1100 1-F	1300 2-F	1500 3-F	1750 4-F	2000 5-F	800 6-F
DAY 7	MEAN	1.2	-2.5	-5.2	--	--	--
	S.D.	0.00	0.00	0.00	--	--	--
	N	1	1	1	0	0	0
DAY 14	MEAN	1.6	5.5	6.6	--	--	--
	S.D.	0.00	0.00	0.00	--	--	--
	N	1	1	1	0	0	0
TOTAL GAIN	MEAN	2.8	3.0	1.4	--	--	--
	S.D.	0.00	0.00	0.00	--	--	--
	N	1	1	1	0	0	0

* P less than .05
 ** P less than .01
 -- = Data Unavailable

Analysis of Variance using DUNNETT'S Procedure

Table 8.4

**ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE**

SUMMARY OF WEIGHT GAINS (Grams)

STUDY: 105PO6A

SEX: FEMALE

PERIOD	DOSE: (mg/kg) GROUP:	0 1-F	0 2-F	800 3-F	1000 4-F
DAY 7	MEAN	2.3	0.9	1.9	0.1
	S.D.	0.80	0.71	1.19	3.50
	N	5	3	3	3
DAY 14	MEAN	-1.7	1.2	0.6	-1.2
	S.D.	3.66	0.99	1.01	7.40
	N	5	3	3	3
TOTAL GAIN	MEAN	0.6	2.1	2.5	-1.1
	S.D.	4.12	1.18	0.21	5.06
	N	5	3	3	3

* P less than .05
** P less than .01

Analysis of Variance using DUNNETT'S Procedure

Table 8.5

**ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE**

SUMMARY OF WEIGHT GAINS (Grams)

STUDY: 105IP26

SEX: FEMALE

PERIOD	DOSE: (mg/kg) GROUP:	100 1-F	120 2-F	140 3-F	170 4-F	200 5-F
DAY 7	MEAN	1.0	1.4	0.8	1.4	-0.1
	S.D.	0.55	0.93	1.08	1.49	1.84
	N	5	5	3	4	2
DAY 14	MEAN	0.5	0.5	1.3	0.7	2.1*
	S.D.	0.40	0.86	0.70	0.42	1.27
	N	5	5	3	4	2
TOTAL GAIN	MEAN	1.4	1.9	2.1	2.1	2.0
	S.D.	0.34	0.99	1.42	1.45	0.57
	N	5	5	3	4	2

* P less than .05
 ** P less than .01

Analysis of Variance using DUNNETT'S Procedure

Table 9

ACUTE ORAL AND INTRAPERITONEAL TOXICITY
STUDY OF WR242511 AND WR269410 IN MICE

Necropsy Observations

WR242511 Tartrate (Gavage)

Dose Level (mg/base/kg)	Males	Females
10	No gross lesions	No gross lesions
13	No gross lesions	No gross lesions
17	No gross lesions	No gross lesions
23	No gross lesions	No gross lesions
30	No gross lesions	No gross lesions

WR242511 (Intraperitoneal)

Dose Level (mg/base/kg)	Males	Females
10	No gross lesions	No gross lesions
13	No gross lesions	No gross lesions
17	No gross lesions	No gross lesions
23	No gross lesions	No gross lesions
30	No gross lesions	No gross lesions

Table 9 (contd.)

ACUTE ORAL AND INTRAPERITONEAL TOXICITY
STUDY OF WR242511 AND WR269410 IN MICE

Necropsy Observations

WR269410 (Gavage; Set 1)

Dose Level (mg/kg)	Males	Females
800	No gross lesions	No gross lesions
1100	No gross lesions	No gross lesions
1300	No gross lesions	No gross lesions
1500	No gross lesions	No gross lesions
1750	No gross lesions	No gross lesions
2000	No gross lesions	No gross lesions

WR269410 (Gavage; Set 2)

Dose Level (mg/base/kg)	Males	Females
Vehicle (10 ml/kg)	Enlarged mesenteric lymph node and subcutaneous cyst for two separate animals	No gross lesions
Vehicle (20 ml/kg)	No gross lesions	No gross lesions
800 (10 ml/kg)	Subcutaneous cyst for one animal	No gross lesions
1000 (10 ml/kg)	No gross lesions	Irregular shaped, pale red-brown lesion of smooth consistency on the left kidney of one animal.

WR269410 (Intraperitoneal)

Dose Level (mg/kg)	Males	Females
100	No gross lesions	No gross lesions
120	No gross lesions	No gross lesions
140	No gross lesions	Fusion of liver & diaphragm in one animal
170	Fusion of liver lobes in one animal	No gross lesions
200	No gross lesions	No gross lesions

Table 10

ACUTE ORAL AND INTRAPERITONEAL TOXICITY
STUDY OF WR242511 AND WR269410 IN MICE

Dose-Mortality Data

WR242511 Tartrate - Gavage

<u>Dose Level (mg base/kg)</u>	<u>Mortality^a</u>	
	<u>Males</u>	<u>Females</u>
10	0/5	0/5
13	0/5	0/5
17	0/5	0/5
23	2/5	3/5
30	5/5	5/5

^anumber of deaths/number of animals in group.

WR242511 Tartrate - Intraperitoneal

<u>Dose Level (mg base/kg)</u>	<u>Mortality^a</u>	
	<u>Males</u>	<u>Females</u>
10	0/5	0/5
13	0/5	0/5
17	0/5	0/5
23	4/5	4/5
30	5/5	5/5

^anumber of deaths/number of animals in group.

Table 10 (contd.)

ACUTE ORAL AND INTRAPERITONEAL TOXICITY
STUDY OF WR242511 AND WR269410 IN MICE

Dose-Mortality Data

WR269410 - Gavage (Set 1)

<u>Dose Level (mg/kg)</u>	<u>Mortality^a</u>	
	<u>Males</u>	<u>Females</u>
800	4/5	5/5
1100	2/5	4/5
1300	3/5	4/5
1500	4/5	4/5
1750	5/5	5/5
2000	4/5	5/5

^anumber of deaths/number of animals in group.

WR269410 - Gavage (Set 2)

<u>Dose Level (mg/kg)</u>	<u>Mortality^a</u>	
	<u>Males</u>	<u>Females</u>
Vehicle (10 ml/kg)	1/5	0/5
Vehicle (20 ml/kg)	1/5	2/5
800	3/5	2/5
1000	1/5	2/5

^anumber of deaths/number of animals in group.

WR269410 -Intraperitoneal

<u>Dose Level (mg base/kg)</u>	<u>Mortality^a</u>	
	<u>Males</u>	<u>Females</u>
100	1/5	0/5
120	4/5	0/5
140	3/5	2/5
170	4/5	1/5
200	5/5	3/5

^anumber of deaths/number of animals in group

APPENDIX 1

Analytical Chemistry Methodology and Dosage Formulation Analysis

INITIAL PURITY AND IDENTITY OF p-AMINOHEPTANOPHENONE (WR269410)
STUDY NO. 105

ANALYSTS: ADAM NEGRUSZ
A. KARL LARSEN, JR.

STUDY SITE: FORENSIC TOXICOLOGY LABORATORY
COLLEGE OF PHARMACY
UNIVERSITY OF ILLINOIS AT CHICAGO
CHICAGO, ILLINOIS 60612

SPONSOR: TOXICOLOGY RESEARCH LABORATORY
UNIVERSITY OF ILLINOIS AT CHICAGO
CHICAGO, ILLINOIS 60612

REPORT PREPARED: JUNE 15, 1993

APPROVED: JUNE 15, 1993
DR. EUGENE F. WOODS, Ph.D.

E.F. Woods

OBJECTIVE

The objective of this study was to confirm the initial identity and establish the purity of WR269410.

EXPERIMENTAL

The subject sample - WR269410 was supplied by the Toxicology Research Laboratory and stored at -20°C when it was not analyzed.

Description

A fine white powder, no obvious odor.

Spectrum

An ultraviolet spectrum (Figure I) recorded on a Shimadzu Spectronic 200 UV spectrometer (dual beam) was obtained from 20 ug/ml solution of WR269410 prepared in mobile phase. The sample was found with maximal absorptivity observed at 230 nm and 312 nm.

PURITY

HPLC System

Solvent Delivery System:	Perkin-Elmer Series 3B Pump
Injector:	Rheodyne 7125 with 20 ul sample loop
Analytical Column:	uBondapak C18, 300 mm x 3.9 mm (Waters)
Detector:	Kratos Spectroflow 773 UV Detector, 0.010 AUFS, 230nm and 312nm
Integrator:	3380A Hewlett-Packard Integrator
Mobile Phase:	60% of acetonitrile and 40% of 0.01 M heptanosulfonate sodium salt in 0.1% (v/v) acetic acid (in water), flow 1.5 ml/minute

Procedure

Six solutions of WR269410 were prepared as follows. Twenty five mg of WR269410 sample was weighed into a 25 ml volumetric flask. The sample was dissolved in and the volume brought to mark

with mobile phase. A 20 ul aliquot of each solution was immediately chromatographed at 230 nm and next at 312 nm.

Results

Typical chromatograms are shown in Figure II. The initial purity study of WR269410 shows that there are no UV absorbing impurities (230 nm, 312 nm) and from this point of view the substance is 100% pure.

IDENTIFICATION

GC-MS System

Gas Chromatograph:	Hewlett-Packard Series II
Mass Selective Detector:	Hewlett-Packard Model 5970
Analytical Column:	30 m x 0.25 mm ID, DB-1 with a 3 micron film thickness.
GC Parameters:	injector temp. 250°C, oven temp. 70°C initial, 280°C final, 20°C/minute ramp, carrier gas - helium, flow rate 2 ml/minute, split ratio 10:1

Procedure

Subject sample (WR269410) was submitted from the Toxicology Research Laboratory. The sample was dissolved in methanol to a concentration of 1 ug/ml and a 2 ul aliquot was injected on the column. The MSD scanned from 40 amu to 400 amu at a rate of 1 scan per second.

Results - GS-MS

The mass spectrum indicates a molecular ion m/e 205 which is in agreement with the WR269410 molecular weight. Major fragments of the sample are m/e 41, 65, 92, 120, 135, 148.

Figure III shows the mass spectrum of the initial WR269410 sample.

FIGURE I

ULTRAVIOLET SPECTRUM OF WR269410

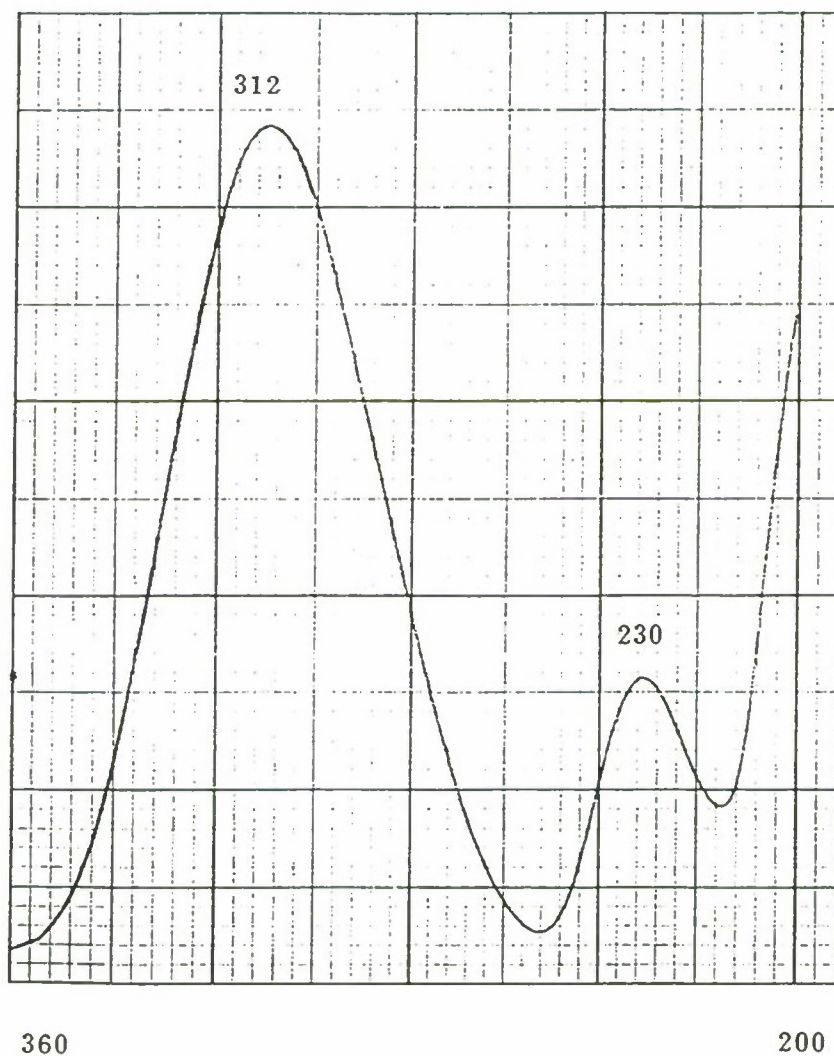
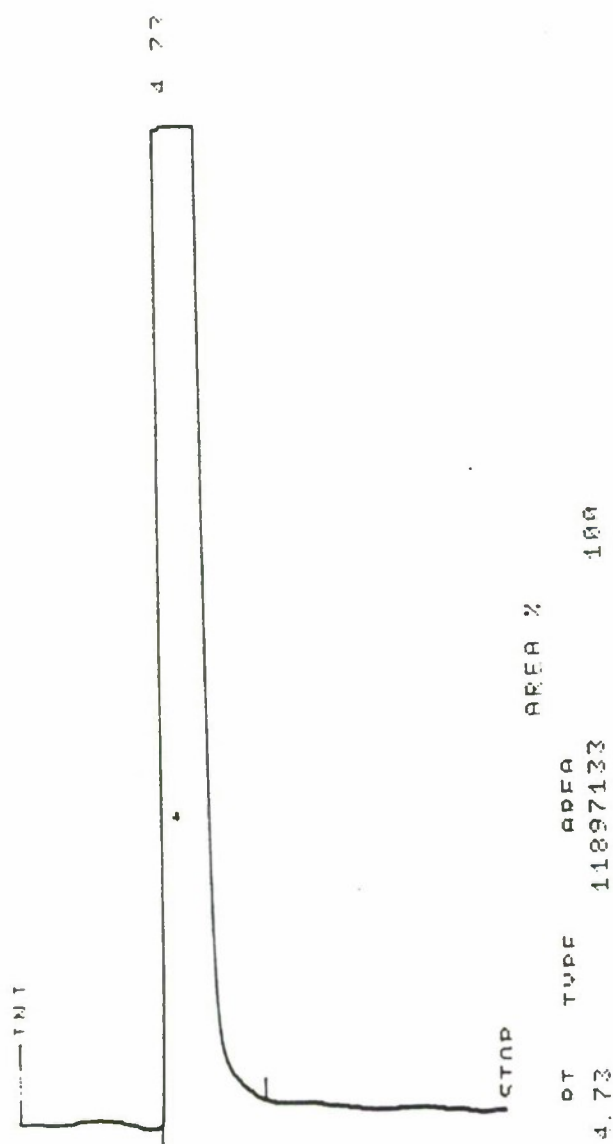
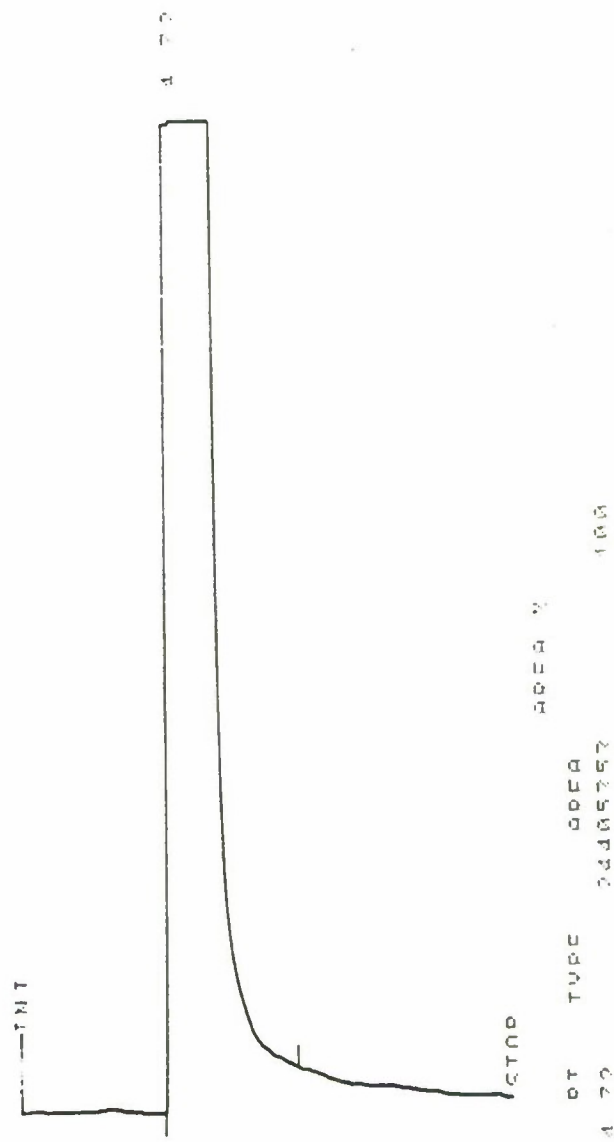


FIGURE II

CHROMATOGRAMS OF WR269410 AT 230 NM
(A) AND 312 NM (B), CONCENTRATION 1 MG/ML



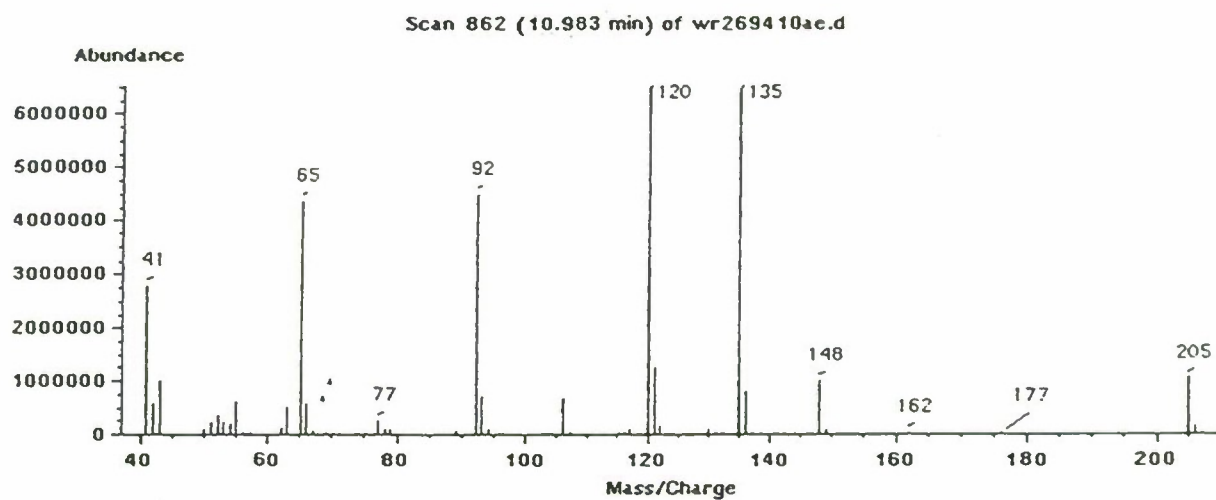
A



B

FIGURE III

MASS SPECTRUM OF INITIAL WR269410 SAMPLE



**INITIAL PURITY AND IDENTITY STUDY AND SAMPLES IN 1% METHYLCELLULOSE AND
0.4% TWEEN 80 ANALYSIS OF 8-[(4-AMINO-1-METHYLBUTYL)AMINO]-5-(1-HEXYLOXY-6-
METHOXY-4-METHYLQUINOLINE DL-TARTRATE (WR242511). STUDY NO. 105**

ANALYSTS: ADAM NEGRUSZ
A.KARL LARSEN, JR.

STUDY SITE: FORENSIC TOXICOLOGY LABORATORY
COLLEGE OF PHARMACY
UNIVERSITY OF ILLINOIS AT CHICAGO
CHICAGO, ILLINOIS 60612

SPONSOR: TOXICOLOGY RESEARCH LABORATORY
UNIVERSITY OF ILLINOIS AT CHICAGO
CHICAGO, ILLINOIS 60612

REPORT PREPARED: JUNE 15, 1993

APPROVED: JUNE 15, 1993
DR. EUGENE F. WOODS, Ph.D.

OBJECTIVE

The objective of this study was to confirm the initial identity, establish the purity of WR242511 and to develop the analytical method for dosage formulation analysis.

WR242511 samples were submitted for analysis April 28, 1993. Results are found on page 9.

In low concentration WR242511 is stable for 48 hours (<10% loss). In high concentration drug is stable during two weeks period of time. This will be reported with the longer term toxicological studies.

EXPERIMENTAL

The subject sample - WR242511 was supplied by the Toxicology Research Laboratory and stored at -20°C when it was not analyzed.

Description

A fine yellow powder, no obvious odor.

Spectrum

An ultraviolet spectrum (Figure I) recorded on a Shimadzu Spectronic 200 UV spectrometer (dual beam), was obtained from 20 ug/ml solution of WR242511 prepared in mobile phase. The sample was found with maximal absorptivity observed at 212 nm and 264 nm.

ANALYTICAL METHOD

Reagents

Subject sample (WR242511) was supplied by Toxicological Research Laboratory. HPLC grade methanol, acetonitrile, ammonium formate and formic acid were purchased from Fisher Scientific. HPLC grade water was supplied through a Millipore, MILLI-Q Reagent Water System which was fed with distilled water.

Standards

All WR242511 concentrations reflect free base value. A 71 mg/ml of base WR242511 stock solution was prepared by weighing 100 mg of DL-tartrate salt (mole fraction = 0.71) into 100 ml volumetric flask. The content was dissolved in and the volume brought to mark with mobile phase. Calibration standard solutions were prepared in mobile phase using 71 mg/ml of base WR242511 stock solution as follows.

<u>Volume Transferred (ml)</u>	<u>Flask Volume (ml)</u>	<u>Final Concentration (ug/ml of base)</u>
1.0	100	7.1
2.0	100	14.2
4.0	100	28.4
6.0	100	42.6
8.0	100	56.8
10.0	100	71.0

Aliquots of 0.5 ml from each calibration standard solution were transferred to individually labelled crimp-top vials, sealed and stored at -20°C until analyzed.

Controls

Control A (0.639 mg/ml of base), control B (2.84 mg/ml of base) and control C (7.81 mg/ml of base) were prepared by weighing 90 mg, 400 mg and 1100 mg respectively of WR242511 DL-tartrate salt into three 100 ml volumetric flasks, dissolved in and diluted to mark with mobile phase. Aliquots of 1.5 ml of each control were transferred to individually labelled screw-capped vials, sealed and stored at -20°C until analyzed.

Analytical Procedure

One set of WR242511 calibration standards and three vials of each stock control solutions were removed from a -20°C freezer to warm up prior to samples analysis. Working control solutions were prepared as follows. Control A - 1 ml of stock solution was transferred to a 25 ml volumetric flask and diluted to mark with mobile phase. Control B - 1 ml of stock solution was transferred to a 25 ml volumetric flask and diluted to mark with mobile phase. Five ml were then transferred to another 25 ml volumetric flask and diluted to mark with mobile phase. Control C was prepared the same way as control B. The standard curve was run at the beginning and at the end of the day. Controls were analyzed in a random order.

HPLC System

See PURITY section, WR242511 was monitored at 230 nm.

Calculations

A standard curve was run at the beginning and the end of the day. Final concentration for controls and samples were determined using a composite standard curve. The composite standard curve was determined by linear least squared regression analysis of the peak areas for WR242511 as a function of concentration. WR242511 concentrations (mg/ml of base) for controls and samples were determined using the following equation:

$$\text{WR242511 conc.} = (Y-B)/M \times (\text{d.f.}/1000)$$

Y - peak area

B - Y-intercept from regression analysis of composite standard curve

M - slope from regression analysis

d.f. - dilution factor

PURITY

HPLC System

Solvent Delivery System:	Perkin-Elmer Series 3B Pump
Injector:	Rheodyne 7125 with 50 ul sample loop
Analytical Column:	Spherisorb CN 5u, 250 mm x 4.6 mm (Alltech)
Detector:	Perkin-Elmer LC-55B UV Detector, 225 nm, 264 nm
Integrator:	Spectra-Physics SP4270 Integrator

Mobile Phase: 20% methanol, 50% acetonitrile, 30% 0.01 M ammonium formate (in water), Ph 3.0 (adjusted with 88% formic acid), flow 1.5 ml/minute

Procedure

Six solutions of WR242511 were prepared as follows. Twenty five mg of WR242511 sample was weighed into a 25 ml volumetric flask. The sample was dissolved in and the volume brought to mark with mobile phase. A 50 ul aliquot of each solution was immediately chromatographed at 225 nm and next at 264 nm.

Calculation of Results

Quantitations were based on the assumption of equal detector response per unit weight of all UV-absorbing components. Areas of WR242511 and other detectable components in the subject sample chromatograms were employed in the following equation to calculate the percentage of WR242511 present in the sample:

$$\% \text{PURITY} = (\text{area of WR242511} / \text{total area}) \times 100$$

Results

Typical chromatogram is shown in Figure II. The subject sample was found to contain less than 1% of one UV-absorbing impurity (225 nm). At 264 nm no visible impurities were observed. Percent purity of WR242511 was found to be 99.51%, standard deviation - 0.02%. The assay results are presented in Table I.

IDENTIFICATION

GC-MS System

Gas Chromatograph: Hewlett-Packard Series II

Mass Selective Detector: Hewlett-Packard Model 5970

Analytical Column: 30 m x 0.25 mm ID, DB-5 with a 3 micron film thickness.

GC Parameters: injector temp. 250°C, oven temp. 70°C initial, 280°C final, 15°C/minute ramp, carrier gas - helium, flow rate 2 ml/minute, split ratio 10:1

Procedure

Subject sample (WR242511) was submitted from the Toxicology Research Laboratory. The sample was dissolved in methanol to a concentration of 0.71 ug/ml of base and a 2 ul aliquot was injected on the column. The MSD scanned from 40 amu to 400 amu at rate of 1 scan per second.

Results - GC-MS

The mass spectrum indicates a molecular ion m/e 373 which is in agreement with the WR242511 molecular weight. Major fragments of WR242511 sample are m/e 84, 175, 203, 288.

Figure III shows the mass spectrum of the initial WR242511 sample.

FIGURE I
ULTRAVIOLET SPECTRUM OF WR242511

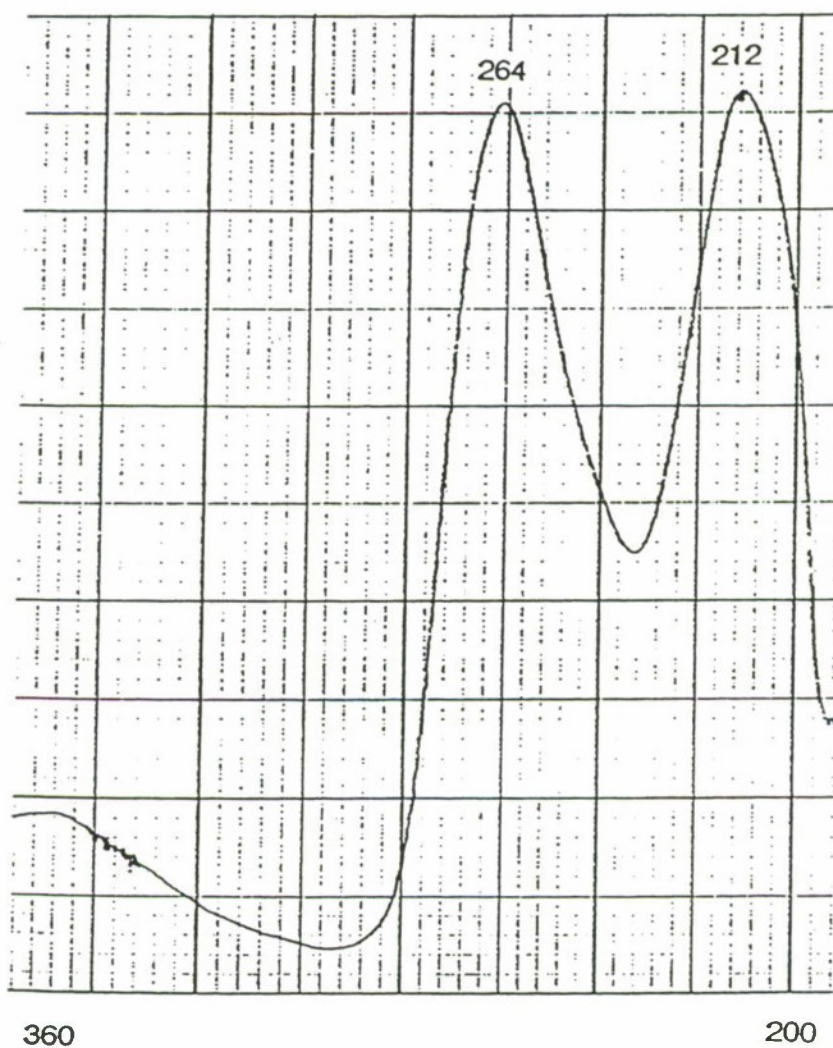


FIGURE II

CHROMATOGRAM OF WR242511 SAMPLE (CONCENTRATION 0.71 MG/ML OF BASE, 225 NM)

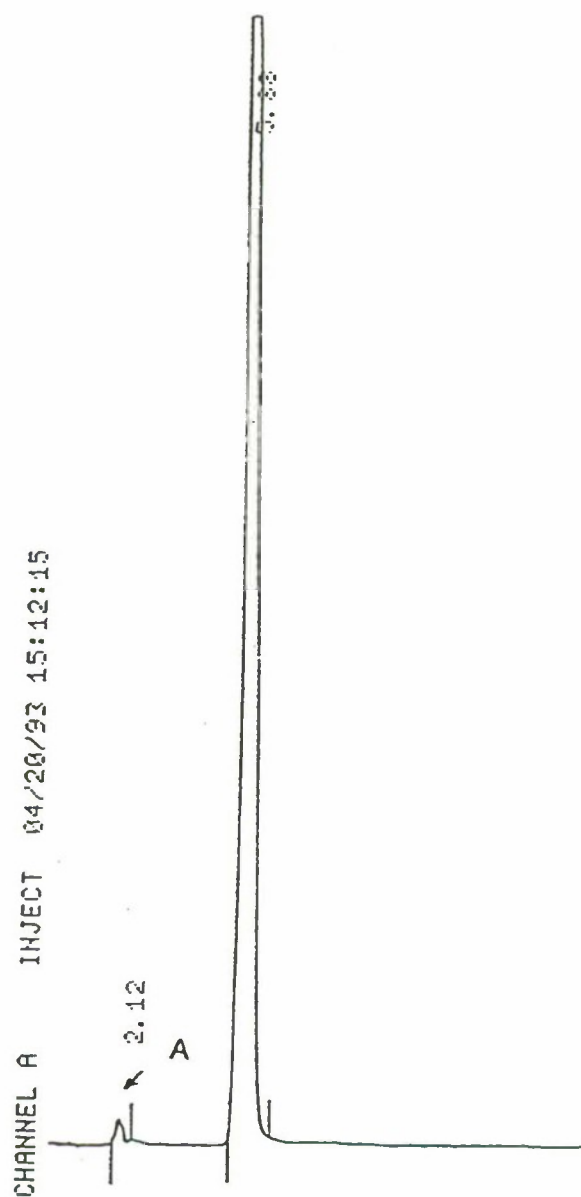


FIGURE III

MASS SPECTRUM OF INITIAL WR242511 SAMPLE

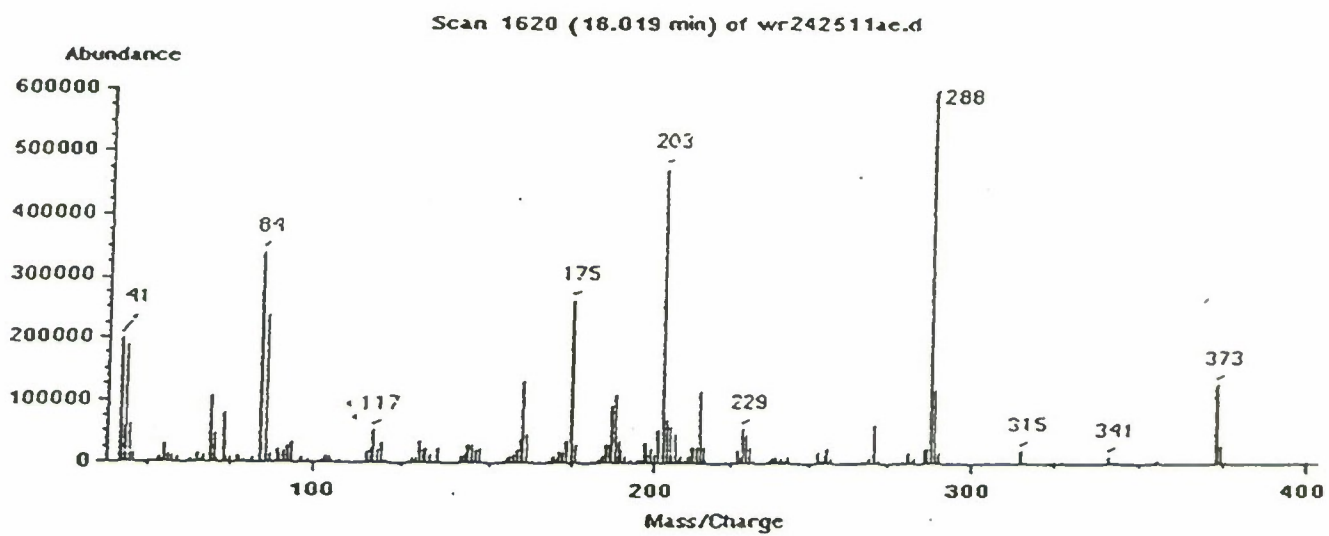


TABLE I

PURITY DATA FOR WR242511 PRIOR TO INITIATING STUDY NO. 105

Solutions

Peak Identity	1	2	3	4	5	6
A	4370	4354	4307	4414	3925	4509
WR242511	871097	863423	869317	869227	872867	862653
% Purity	99.501	99.498	99.507	99.495	99.552	99.480

Mean \pm S.D. - 99.505 \pm 0.024

MEMO

DATE: April 28, 1993
TO: Dr. Barry S. Levine
FROM: Adam Negrusz
Forensic Toxicology Laboratory
College of Pharmacy
RE: WR242511 samples submitted for analysis April 28, 1993.

WR242511 Concentration (mg/ml of base)

Sample
Identification

Mean (\pm SD)

PINK WITH BLACK DOT (3.0)	2.9738 (\pm 0.0061)
GREEN WITH YELLOW DOT (2.3)	2.3230 (\pm 0.0437)
BLUE WITH YELLOW DOT (1.7)	1.6939 (\pm 0.0297)
ORANGE WITH YELLOW DOT (1.3)	1.3064 (\pm 0.0070)
GREEN WITH BLUE DOT (1.0)	0.9893 (\pm 0.0133)
PINK (6.0)	4.8198 (\pm 0.0179)
PINK AFTER ADJUSTMENT	5.8143 (\pm 0.0037)
GREEN (4.6)	4.5849 (\pm 0.0336)
BLUE (3.4)	3.3920 (\pm 0.0411)
ORANGE (2.6)	2.5483 (\pm 0.0203)
LIGHT GREEN (2.0)	2.1742 (\pm 0.0096)

APPENDIX 2

Analytical Chemistry Report
from Dr. Flanagan (Univ. of Iowa)

**Analysis of p-Aminoheptanophenone (WR269410) Solutions in PEG 200
After Toxicological Testing**

Douglas R. Flanagan, Ph.D.
Siriporn Toongsuwan, B.S.
Kirk VanDer Kamp, B.S.

July 21, 1993

Contract No. DAMD 17-92-C-2035

College of Pharmacy
University of Iowa
Iowa City, IA 52242
(319) 335-8824

**Analysis of p-Aminoheptanophenone (WR269410) Solution in PEG 200
After Toxicological Testing**

Summary

PEG 200 solutions of WR269410 were analyzed for content after receipt from the University of Illinois (Dr. Barry Levine).

Assay Procedure

1. Make fresh standard solution (about 10 µg/mL) of PAHP in 95% ethanol.
2. Dilute PAHP in PEG 200 solutions that were send from UIC with 95% ethanol (dilution factor = 10,000) by diluting 1 mL of the sample to 100 mL and then diluting 1 mL of this solution to 100 mL with 95% ethanol.
3. Assay the concentration of the solutions by using the HP 8450 UV spectrophotometer.
4. Concentration of the samples were calculated as follow:

$$\text{sample conc.} = (\text{std conc.} * \text{Abs}_{\text{sample}}) * 10,000 / \text{Abs}_{\text{std}}$$

Assay Results

The results from the UV assay of PAHP solutions are shown in Tables 1, 2 and 3.

Table 1: UV Assay Data of PAHP Solutions Returned from UIC on 05/21/93; Mouse Study

Labeled Conc. (mg/mL)	Experimental Conc. (mg/mL)
20	18.2
24	26.4
28	31.3
34	31.7
40	40.3
55	50.3
65	66.8
75	77.6
87.5	84.2

TABLE 2: UV Assay Data of PAHP Solutions Returned from UIC on
07/08/93; Rat Study

Labeled Conc. (mg/mL)	Experimental Conc. (mg/mL)
6	6.9
12	8.5
25	26.7
50	42.9
100	94.5

TABLE 3: UV Assay Data of PAHP Solutions Returned from UIC on
07/08/93; Mouse Study

Labeled Conc. (mg/mL)	Experimental Conc. (mg/mL)
80	73.2

APPENDIX 3

Individual Observations

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO24
DAY 0-DAY 14

GROUP: 1-M
DOSE: 10 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
201	Normal		DAY	1-DAY 13
	Normal #1		DAY	0
	Normal #2		DAY	0
	Normal #3		DAY	0
	Scheduled Sacrifice		DAY	14
202	Normal		DAY	1-DAY 11
	Normal		DAY	13
	Normal #1		DAY	0
	Normal #2		DAY	0
	Normal #3		DAY	0
	Rough Coat		DAY	12
	Scheduled Sacrifice		DAY	14
203	Normal		DAY	1-DAY 11
	Normal		DAY	13
	Normal #1		DAY	0
	Normal #2		DAY	0
	Normal #3		DAY	0
	Rough Coat		DAY	12
	Scheduled Sacrifice		DAY	14
204	Normal		DAY	1-DAY 13
	Normal #1		DAY	0
	Normal #2		DAY	0
	Normal #3		DAY	0
	Scheduled Sacrifice		DAY	14
205	Normal		DAY	1-DAY 13
	Normal #1		DAY	0
	Normal #2		DAY	0
	Normal #3		DAY	0
	Scheduled Sacrifice		DAY	14

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO24
DAY 0-DAY 14

GROUP: 2-M
DOSE: 13(mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
211	Normal			DAY 1-DAY 3
	Normal			DAY 5-DAY 13
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 4
	Scheduled Sacrifice			DAY 14
212	Normal			DAY 1-DAY 3
	Normal			DAY 7-DAY 11
	Normal			DAY 13
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 4-DAY 6
	Rough Coat			DAY 12
	Scheduled Sacrifice			DAY 14
213	Normal			DAY 1-DAY 13
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Scheduled Sacrifice			DAY 14
214	Normal			DAY 1-DAY 13
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Scheduled Sacrifice			DAY 14
215	Normal			DAY 1-DAY 3
	Normal			DAY 6-DAY 11
	Normal			DAY 13
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 4-DAY 5
	Rough Coat			DAY 12
	Scheduled Sacrifice			DAY 14

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO24
DAY 0-DAY 14

GROUP: 3-M
DOSE: 17 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
221	Normal		DAY 1-DAY 3	
	Normal		DAY 5-DAY 13	
	Normal #1		DAY 0	
	Normal #2		DAY 0	
	Normal #3		DAY 0	
	Rough Coat		DAY 4	
	Scheduled Sacrifice		DAY 14	
222	Normal		DAY 1-DAY 13	
	Normal #1		DAY 0	
	Normal #2		DAY 0	
	Normal #3		DAY 0	
	Scheduled Sacrifice		DAY 14	
223	Normal		DAY 1-DAY 11	
	Normal		DAY 13	
	Normal #1		DAY 0	
	Normal #2		DAY 0	
	Normal #3		DAY 0	
	Rough Coat		DAY 12	
	Scheduled Sacrifice		DAY 14	
224	Normal		DAY 1-DAY 4	
	Normal		DAY 11	
	Normal		DAY 13	
	Normal #1		DAY 0	
	Normal #2		DAY 0	
	Normal #3		DAY 0	
	Rough Coat		DAY 5-DAY 10	
	Rough Coat		DAY 12	
	Scheduled Sacrifice		DAY 14	
225	Normal		DAY 1-DAY 4	
	Normal		DAY 6-DAY 11	
	Normal		DAY 13	
	Normal #1		DAY 0	
	Normal #2		DAY 0	

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO24
DAY 0-DAY 14

GROUP: 3-M
DOSE: 17 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
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225 (contd.)	Normal #3			DAY 0
	Rough Coat			DAY 5
	Rough Coat			DAY 12
	Scheduled Sacrifice			DAY 14

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO24
DAY 0-DAY 14

GROUP: 4-M
DOSE: 23 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
231	Normal			DAY 1-DAY 4
	Normal			DAY 6-DAY 11
	Normal			DAY 13
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 5
	Rough Coat			DAY 12
	Scheduled Sacrifice			DAY 14
232	Activity Decreased	1		DAY 3
	Ataxia	1		DAY 3
	Animal Found Dead			DAY 4
	Normal			DAY 1
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 2-DAY 3
233	Activity Decreased	1		DAY 3-DAY 4
	Activity Decreased	1		DAY 6
	Animal Found Dead			DAY 6
	Hunched Posture			DAY 5-DAY 6
	Lethargic			DAY 5
	Normal			DAY 1
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 2-DAY 6
234	Normal			DAY 1-DAY 13
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Scheduled Sacrifice			DAY 14
235	Normal			DAY 1-DAY 11

Severity Codes

Severity No.	Description
1	Slight
2	Moderate
3	Severe

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO24
DAY 0-DAY 14

GROUP: 4-M
DOSE: 23 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
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235 (contd.)	Normal			DAY 13
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 12
	Scheduled Sacrifice			DAY 14

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO24
DAY 0-DAY 14

GROUP: 5-M
DOSE: 30(mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
241	Animal Found Dead			DAY 2
	Normal			DAY 1
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
242	Animal Found Dead			DAY 3
	Normal			DAY 1
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 2
243	Animal Found Dead			DAY 3
	Normal			DAY 1
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 2
244	Animal Found Dead			DAY 4
	Lethargic			DAY 3
	Normal			DAY 1
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 2-DAY 3
245	Comatose			DAY 2
	Animal Found Dead			DAY 2
	Normal			DAY 1
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105IP24
DAY 0-DAY 14

GROUP: 1-M
DOSE: 10 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
251	Normal			DAY 1-DAY 11
	Normal			DAY 13
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 12
	Scheduled Sacrifice			DAY 14
252	Normal			DAY 0-DAY 4
	Normal			DAY 6-DAY 11
	Normal			DAY 13
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 5
	Rough Coat			DAY 12
	Scheduled Sacrifice			DAY 14
253	Normal			DAY 0-DAY 11
	Normal			DAY 13
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 12
	Scheduled Sacrifice			DAY 14
254	Normal			DAY 0-DAY 11
	Normal			DAY 13
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 12
	Scheduled Sacrifice			DAY 14
255	Normal			DAY 0-DAY 11
	Normal			DAY 13
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 12
	Scheduled Sacrifice			DAY 14

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105IP24
DAY 0-DAY 14

GROUP: 2-M
DOSE: 13 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
261	Normal			DAY 0-DAY 7
	Normal			DAY 11
	Normal			DAY 13
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 8-DAY 10
	Rough Coat			DAY 12
	Scheduled Sacrifice			DAY 14
262	Normal			DAY 1-DAY 9
	Normal			DAY 11
	Normal			DAY 13
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 10
	Rough Coat			DAY 12
	Scheduled Sacrifice			DAY 14
263	Normal			DAY 1-DAY 8
	Normal			DAY 10-DAY 11
	Normal			DAY 13
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 9
	Rough Coat			DAY 12
	Scheduled Sacrifice			DAY 14
264	Normal			DAY 1-DAY 9
	Normal			DAY 11-DAY 13
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 10
	Scheduled Sacrifice			DAY 14

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105IP24
DAY 0-DAY 14

GROUP: 2-M
DOSE: 13(mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
265	Normal			DAY 1-DAY 4
	Normal			DAY 6-DAY 11
	Normal			DAY 13
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 5
	Rough Coat			DAY 12
	Scheduled Sacrifice			DAY 14

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105IP24
DAY 0-DAY 14

GROUP: 3-M
DOSE: 17(mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
271	Normal			DAY 1
	Normal			DAY 3-DAY 7
	Normal			DAY 11
	Normal			DAY 13
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 2
	Rough Coat			DAY 8-DAY 10
	Rough Coat			DAY 12
	Scheduled Sacrifice			DAY 14
272	Normal			DAY 1
	Normal			DAY 3-DAY 5
	Normal			DAY 7-DAY 8
	Normal			DAY 10-DAY 11
	Normal			DAY 13
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 2
	Rough Coat			DAY 6
	Rough Coat			DAY 9
	Rough Coat			DAY 12
	Scheduled Sacrifice			DAY 14
273	Normal			DAY 1-DAY 5
	Normal			DAY 7-DAY 9
	Normal			DAY 11
	Normal			DAY 13
	Normal #1			DAY 0
				DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 6
	Rough Coat			DAY 10
	Rough Coat			DAY 12
	Scheduled Sacrifice			DAY 14

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105IP24
DAY 0-DAY 14

GROUP: 3-M
DOSE: 17(mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
274	Normal			DAY 1
	Normal			DAY 3
	Normal			DAY 5-DAY 7
	Normal			DAY 11
	Normal			DAY 13
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 2
	Rough Coat			DAY 4
	Rough Coat			DAY 8-DAY 10
	Rough Coat			DAY 12
	Scheduled Sacrifice			DAY 14
275	Normal			DAY 1-DAY 4
	Normal			DAY 6-DAY 9
	Normal			DAY 11
	Normal			DAY 13
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 5
	Rough Coat			DAY 10
	Rough Coat			DAY 12
	Scheduled Sacrifice			DAY 14

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105IP24
DAY 0-DAY 14

GROUP: 4-M
DOSE: 23 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
281	Animal Found Dead			DAY 3
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 1-DAY 2
282	Animal Found Dead			DAY 3
	Normal			DAY 1
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 2
283	Normal			DAY 1
	Normal			DAY 7
	Normal			DAY 11
	Normal			DAY 13
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 2-DAY 6
	Rough Coat			DAY 8-DAY 10
	Rough Coat			DAY 12
	Scheduled Sacrifice			DAY 14
284	Activity Decreased	1		DAY 3-DAY 4
	Animal Found Dead			DAY 4
	Hunched Posture			DAY 3-DAY 4
	Normal			DAY 1
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 2-DAY 4
285	Animal Found Dead			DAY 3
	Hunched Posture			DAY 2
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 1-DAY 2

Severity Codes

Severity No.	Description
1	Slight
2	Moderate
3	Severe

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105IP24
DAY 0-DAY 14

GROUP: 5-M
DOSE: 30 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
291	Ataxia Animal Found Dead Normal #1 Normal #2 Normal #3 Rough Coat	1		DAY 3 DAY 4 DAY 0 DAY 0 DAY 0 DAY 1-DAY 3
292	Activity Decreased Ataxia Animal Found Dead Hunched Posture Normal #1 Normal #2 Normal #3 Rough Coat	1 1		DAY 3-DAY 5 DAY 5 DAY 5 DAY 5 DAY 0 DAY 0 DAY 0 DAY 1-DAY 5
293	Activity Decreased Animal Found Dead Normal #1 Normal #2 Normal #3 Rough Coat	1		DAY 1-DAY 2 DAY 3 DAY 0 DAY 0 DAY 0 DAY 2
294	Activity Decreased Animal Found Dead Normal #1 Normal #2 Normal #3 Rough Coat	1		DAY 2 DAY 3 DAY 1 DAY 0 DAY 0 DAY 0 DAY 2
295	Activity Decreased Animal Found Dead Normal #1 Normal #2 Normal #3	1		DAY 2 DAY 3 DAY 1 DAY 0 DAY 0 DAY 0

Severity Codes

Severity No.	Description
1	Slight
2	Moderate
3	Severe

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO26
DAY 0-DAY 14

GROUP: 1-M
DOSE: 1100 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
301	Activity Decreased #1	1		DAY 0
	Activity Decreased #2	1		DAY 0
	Activity Decreased #3	1		DAY 0
	Normal			DAY 4
	Normal			DAY 6
	Normal			DAY 13
	Rough Coat			DAY 1-DAY 3
	Rough Coat			DAY 5
	Rough Coat			DAY 7-DAY 12
	Rough Coat #3			DAY 0
	Scheduled Sacrifice			DAY 14
302	Comatose #2			DAY 0
	Comatose #3			DAY 0
	Animal Found Dead			DAY 1
	Lethargic #1			DAY 0
303	Activity Decreased #1	1		DAY 0
	Activity Decreased #2	2		DAY 0
	Activity Decreased #3	2		DAY 0
	Animal Found Dead			DAY 1
	Rough Coat #3			DAY 0
304	Activity Decreased #1	1		DAY 0
	Activity Decreased #2	1		DAY 0
	Activity Decreased #3	1		DAY 0
	Normal			DAY 11
	Rough Coat			DAY 1-DAY 10
	Rough Coat			DAY 12-DAY 13
	Rough Coat #1			DAY 0
	Rough Coat #2			DAY 0
	Rough Coat #3			DAY 0
	Scheduled Sacrifice			DAY 14
305	Activity Decreased #1	1		DAY 0
	Activity Decreased #2	1		DAY 0
	Activity Decreased #3	1		DAY 0

Severity Codes

Severity No.	Description
1	Slight
2	Moderate
3	Severe

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO26
DAY 0-DAY 14

GROUP: 1-M
DOSE: 1100 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
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305 (contd.)	Normal			DAY 4
	Normal			DAY 6
	Normal			DAY 11
	Normal			DAY 13
	Rough Coat			DAY 1-DAY 3
	Rough Coat			DAY 5
	Rough Coat			DAY 7-DAY 10
	Rough Coat			DAY 12
	Rough Coat #3			DAY 0
	Scheduled Sacrifice			DAY 14

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO26
DAY 0-DAY 14

GROUP: 2-M
DOSE: 1300 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
311	Activity Decreased	1	DAY	5
	Activity Decreased #1	1	DAY	0
	Activity Decreased #2	1	DAY	0
	Activity Decreased #3	1	DAY	0
	Hunched Posture		DAY	5
	Normal		DAY	11-DAY 13
	Rough Coat		DAY	1-DAY 10
	Rough Coat #2		DAY	0
	Rough Coat #3		DAY	0
	Scheduled Sacrifice		DAY	14
312	Activity Decreased #1	1	DAY	0
	Activity Decreased #2	1	DAY	0
	Activity Decreased #3	1	DAY	0
	Animal Found Dead		DAY	1
	Rough Coat #2		DAY	0
	Rough Coat #3		DAY	0
313	Comatose #2		DAY	0
	Comatose #3		DAY	0
	Animal Found Dead		DAY	1
	Lethargic #1		DAY	0
314	Animal Found Dead		DAY	1
	Lethargic #1		DAY	0
	Lethargic #2		DAY	0
	Lethargic #3		DAY	0
315	Activity Decreased #1	1	DAY	0
	Normal		DAY	4
	Normal		DAY	11
	Normal		DAY	13
	Rough Coat		DAY	1-DAY 3
	Rough Coat		DAY	5-DAY 10
	Rough Coat		DAY	12
	Rough Coat #1		DAY	0
	Rough Coat #2		DAY	0
	Rough Coat #3		DAY	0
	Scheduled Sacrifice		DAY	14

Severity Codes

Severity No.	Description
1	Slight
2	Moderate
3	Severe

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO26
DAY 0-DAY 14

GROUP: 3-M
DOSE: 1500 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
321	Activity Decreased #1	1		DAY 0
	Activity Decreased #2	1		DAY 0
	Activity Decreased #3	1		DAY 0
	Hunched Posture			DAY 5-DAY 6
	Normal			DAY 12-DAY 13
	Rough Coat			DAY 1-DAY 11
	Rough Coat #1			DAY 0
	Rough Coat #2			DAY 0
	Rough Coat #3			DAY 0
	Scheduled Sacrifice			DAY 14
322	Comatose #1			DAY 0
	Comatose #2			DAY 0
	Animal Found Dead			DAY 1
	Lethargic #3			DAY 0
323	Activity Decreased #1	1		DAY 0
	Animal Found Dead			DAY 1
	Lethargic #2			DAY 0
	Lethargic #3			DAY 0
324	Comatose #2			DAY 0
	Comatose #3			DAY 0
	Activity Decreased #1	2		DAY 0
	Animal Found Dead			DAY 1
325	Activity Decreased #3	2		DAY 0
	Animal Found Dead			DAY 1
	Lethargic #1			DAY 0
	Lethargic #2			DAY 0

Severity Codes

<u>Severity No.</u>	<u>Description</u>
1	Slight
2	Moderate
3	Severe

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO26
DAY 0-DAY 14

GROUP: 4-M
DOSE: 1750 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
331	Activity Decreased #2	3		DAY 0
	Activity Decreased #3	3		DAY 0
	Animal Found Dead			DAY 1
	Lethargic #1			DAY 0
332	Activity Decreased #1	3		DAY 0
	Animal Found Dead			DAY 1
	Lethargic #2			DAY 0
	Lethargic #3			DAY 0
333	Activity Decreased #1	1		DAY 0
	Activity Decreased #2	2		DAY 0
	Animal Found Dead			DAY 1
	Lethargic #3			DAY 0
334	Comatose #1			DAY 0
	Comatose #2			DAY 0
	Comatose #3			DAY 0
	Animal Found Dead			DAY 1
335	Activity Decreased #1	3		DAY 0
	Animal Found Dead			DAY 1
	Lethargic #2			DAY 0
	Lethargic #3			DAY 0

Severity Codes

<u>Severity No.</u>	<u>Description</u>
1	Slight
2	Moderate
3	Severe

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO26
DAY 0-DAY 14

GROUP: 5-M
DOSE: 2000 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
341	Activity Decreased #1	1		DAY 0
	Activity Decreased #3	2		DAY 0
	Animal Found Dead			DAY 1
	Lethargic			DAY 1
	Lethargic #2			DAY 0
	Rough Coat			DAY 1
	Rough Coat #3			DAY 0
342	Comatose #1			DAY 0
	Comatose #2			DAY 0
	Comatose #3			DAY 0
	Animal Found Dead			DAY 1
343	Activity Decreased	1		DAY 6
	Activity Decreased #2	1		DAY 0
	Activity Decreased #3	1		DAY 0
	Hunched Posture			DAY 5-DAY 6
	Normal			DAY 11-DAY 13
	Rough Coat			DAY 1-DAY 10
	Rough Coat #1			DAY 0
	Rough Coat #2			DAY 0
	Rough Coat #3			DAY 0
	Scheduled Sacrifice			DAY 14
344	Comatose			DAY 1
	Animal Found Dead			DAY 1
	Lethargic #1			DAY 0
	Lethargic #2			DAY 0
	Lethargic #3			DAY 0
345	Comatose #1			DAY 0
	Comatose #2			DAY 0
	Comatose #3			DAY 0
	Animal Found Dead			DAY 1

Severity Codes

<u>Severity No.</u>	<u>Description</u>
1	Slight
2	Moderate
3	Severe

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO26
DAY 0-DAY 14

GROUP: 6-M
DOSE: 800 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
401	Animal Found Dead			DAY 1
	Lethargic #1			DAY 0
	Lethargic #2			DAY 0
	Lethargic #3			DAY 0
402	Activity Decreased #1	1		DAY 0
	Activity Decreased #2	1		DAY 0
	Activity Decreased #3	1		DAY 0
	Animal Found Dead			DAY 2
	Lethargic			DAY 1
	Rough Coat			DAY 1-DAY 2
	Rough Coat #1			DAY 0
	Rough Coat #2			DAY 0
	Rough Coat #3			DAY 0
403	Activity Decreased	1		DAY 1
	Activity Decreased #1	1		DAY 0
	Activity Decreased #2	1		DAY 0
	Activity Decreased #3	1		DAY 0
	Normal			DAY 3
	Normal			DAY 7-DAY 8
	Normal			DAY 10-DAY 13
	Rough Coat			DAY 1-DAY 2
	Rough Coat			DAY 4-DAY 6
	Rough Coat			DAY 9
	Rough Coat #1			DAY 0
	Rough Coat #2			DAY 0
	Rough Coat #3			DAY 0
	Scheduled Sacrifice			DAY 14
404	Animal Found Dead			DAY 1
	Lethargic #1			DAY 0
	Lethargic #2			DAY 0
	Lethargic #3			DAY 0
405	Activity Decreased #3	2		DAY 0
	Animal Found Dead			DAY 1
	Lethargic #1			DAY 0
	Lethargic #2			DAY 0
	Rough Coat #3			DAY 0

Severity Codes

<u>Severity No.</u>	<u>Description</u>
1	Slight
2	Moderate
3	Severe

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO6A
DAY 0-DAY 14

GROUP: 1-M
DOSE: 0 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
631	Normal Normal Normal 1 Normal 2 Normal 3 Rough Coat Scheduled Sacrifice			DAY 1-DAY 8 DAY 12-DAY 13 DAY 0 DAY 0 DAY 0 DAY 9-DAY 11 DAY 14
632	Normal Normal Normal 1 Normal 2 Normal 3 Rough Coat Scheduled Sacrifice			DAY 1-DAY 6 DAY 8-DAY 13 DAY 0 DAY 0 DAY 0 DAY 7 DAY 14
633	Normal Normal Normal 1 Normal 2 Normal 3 Rough Coat Rough Coat Scheduled Sacrifice			DAY 1-DAY 2 DAY 5-DAY 12 DAY 0 DAY 0 DAY 0 DAY 3-DAY 4 DAY 13 DAY 14
634	Normal Normal Normal 1 Normal 2 Normal 3 Rough Coat Scheduled Sacrifice			DAY 1-DAY 4 DAY 8-DAY 13 DAY 0 DAY 0 DAY 0 DAY 5-DAY 7 DAY 14
635	Decreased Activity Decreased Activity 1 Decreased Activity 2 Decreased Activity 3	1 1 1 2		DAY 1 DAY 0 DAY 0 DAY 0

Severity Codes

<u>Severity No.</u>	<u>Description</u>
1	Slight
2	Moderate
3	Severe

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO6A
DAY 0-DAY 14

GROUP: 1-M
DOSE: 0 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
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635 (contd.)	Animal Found Dead			DAY 2
	Hunched Posture			DAY 1
	Rough Coat			DAY 1
	Rough Coat 1			DAY 0
	Rough Coat 2			DAY 0
	Rough Coat 3			DAY 0

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO6A
DAY 0-DAY 14

GROUP: 2-M
DOSE: 0 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
611	Hunched Posture			DAY 4
	Normal			DAY 1-DAY 3
	Normal			DAY 5-DAY 8
	Normal			DAY 12
	Rough Coat			DAY 4
	Rough Coat			DAY 9-DAY 11
	Rough Coat			DAY 13
	Rough Coat 1			DAY 0
	Rough Coat 2			DAY 0
	Rough Coat 3			DAY 0
	Scheduled Sacrifice			DAY 14
612	Hunched Posture			DAY 4
	Hunched Posture 1			DAY 0
	Normal			DAY 1-DAY 2
	Normal			DAY 5-DAY 10
	Normal			DAY 12
	Rough Coat			DAY 3-DAY 4
	Rough Coat			DAY 11
	Rough Coat			DAY 13
	Rough Coat 1			DAY 0
	Rough Coat 2			DAY 0
	Rough Coat 3			DAY 0
	Scheduled Sacrifice			DAY 14
613	Normal			DAY 5
	Normal			DAY 7-DAY 10
	Normal			DAY 13
	Rough Coat			DAY 1-DAY 4
	Rough Coat			DAY 6
	Rough Coat			DAY 11-DAY 12
	Rough Coat 1			DAY 0
	Rough Coat 2			DAY 0
	Rough Coat 3			DAY 0
	Scheduled Sacrifice			DAY 14
614	Normal			DAY 1-DAY 2

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO6A
DAY 0-DAY 14

GROUP: 2-M
DOSE: 0 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
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614 (contd.)

Normal
Normal
Rough Coat
Rough Coat
Rough Coat
Rough Coat 1
Rough Coat 2
Rough Coat 3
Scheduled Sacrifice

DAY 6
DAY 12
DAY 3-DAY 5
DAY 7-DAY 11
DAY 13
DAY 0
DAY 0
DAY 0
DAY 14

615

Animal Found Dead

DAY 0

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105P06A
DAY 0-DAY 14

GROUP: 3-M
DOSE: 800 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
621	Decreased Activity 2	1		DAY 0
	Hunched Posture			DAY 2
	Normal			DAY 1
	Normal			DAY 5-DAY 13
	Normal 1			DAY 0
	Rough Coat			DAY 2-DAY 4
	Rough Coat 2			DAY 0
	Rough Coat 3			DAY 0
	Scheduled Sacrifice			DAY 14
622	Decreased Activity 1	1		DAY 0
	Decreased Activity 2	2		DAY 0
	Decreased Activity 3	2		DAY 0
	Animal Found Dead			DAY 1
	Rough Coat 1			DAY 0
	Rough Coat 2			DAY 0
	Rough Coat 3			DAY 0
623	Decreased Activity 1	1		DAY 0
	Decreased Activity 2	2		DAY 0
	Decreased Activity 3	2		DAY 0
	Animal Found Dead			DAY 1
	Rough Coat 1			DAY 0
	Rough Coat 2			DAY 0
	Rough Coat 3			DAY 0
624	Normal			DAY 11
	Rough Coat			DAY 1-DAY 10
	Rough Coat			DAY 12-DAY 13
	Rough Coat 1			DAY 0
	Rough Coat 2			DAY 0
	Rough Coat 3			DAY 0
	Scheduled Sacrifice			DAY 14
625	Animal Found Dead			DAY 0

Severity Codes

Severity No.	Description
1	Slight
2	Moderate
3	Severe

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO6A
DAY 0-DAY 14

GROUP: 4-M
DOSE: 1000 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
601	Decreased Activity 3	1		DAY 0
	Hunched Posture			DAY 1
	Hunched Posture			DAY 4-DAY 5
	Hunched Posture 1			DAY 0
	Normal			DAY 2
	Normal			DAY 6
	Normal			DAY 9-DAY 12
	Rough Coat			DAY 1
	Rough Coat			DAY 3-DAY 5
	Rough Coat			DAY 7-DAY 8
	Rough Coat			DAY 13
	Rough Coat 1			DAY 0
	Rough Coat 2			DAY 0
	Rough Coat 3			DAY 0
	Scheduled Sacrifice			DAY 14
602	Hunched Posture			DAY 1-DAY 7
	Hunched Posture			DAY 13
	Hunched Posture 1			DAY 0
	Hunched Posture 2			DAY 0
	Hunched Posture 3			DAY 0
	Normal			DAY 8
	Rough Coat			DAY 1-DAY 7
	Rough Coat			DAY 9-DAY 13
	Rough Coat 1			DAY 0
	Rough Coat 2			DAY 0
	Rough Coat 3			DAY 0
	Scheduled Sacrifice			DAY 14
603	Animal Found Dead			DAY 0
604	Decreased Activity	1		DAY 3-DAY 4
	Decreased Activity 1	1		DAY 0
	Decreased Activity 2	1		DAY 0
	Decreased Activity 3	1		DAY 0
	Hunched Posture			DAY 1-DAY 4
	Hunched Posture 1			DAY 0

Severity Codes

Severity No.	Description
1	Slight
2	Moderate
3	Severe

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO6A
DAY 0-DAY 14

GROUP: 4-M
DOSE: 1000 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
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604 (contd.)	Hunched Posture 2			DAY 0
	Hunched Posture 3			DAY 0
	Normal			DAY 5-DAY 6
	Normal			DAY 9-DAY 12
	Rough Coat			DAY 1-DAY 4
	Rough Coat			DAY 7-DAY 8
	Rough Coat			DAY 13
	Rough Coat 1			DAY 0
	Rough Coat 2			DAY 0
	Rough Coat 3			DAY 0
	Scheduled Sacrifice			DAY 14
605	Decreased Activity 1	1		DAY 0
	Hunched Posture			DAY 1
	Hunched Posture			DAY 3-DAY 5
	Hunched Posture 1			DAY 0
	Hunched Posture 2			DAY 0
	Normal			DAY 2
	Normal			DAY 8
	Normal			DAY 11-DAY 13
	Rough Coat			DAY 1
	Rough Coat			DAY 3-DAY 7
	Rough Coat			DAY 9-DAY 10
	Rough Coat 1			DAY 0
	Rough Coat 2			DAY 0
	Rough Coat 3			DAY 0
	Scheduled Sacrifice			DAY 14

Severity Codes

<u>Severity No.</u>	<u>Description</u>
1	Slight
2	Moderate
3	Severe

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105IP26
DAY 0-DAY 14

GROUP: 1-M
DOSE: 100 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
351	Activity Decreased #1	2		DAY 0
	Activity Decreased #2	1		DAY 0
	Activity Decreased #3	1		DAY 0
	Normal			DAY 6
	Normal			DAY 11
	Normal			DAY 13
	Rough Coat			DAY 1-DAY 5
	Rough Coat			DAY 7-DAY 10
	Rough Coat			DAY 12
	Rough Coat #1			DAY 0
	Rough Coat #2			DAY 0
	Rough Coat #3			DAY 0
	Scheduled Sacrifice			DAY 14
352	Activity Decreased #2	2		DAY 0
	Activity Decreased #3	1		DAY 0
	Animal Found Dead			DAY 5
	Lethargic #1			DAY 0
	Rough Coat			DAY 1-DAY 4
	Rough Coat #2			DAY 0
	Rough Coat #3			DAY 0
353	Activity Decreased #1	1		DAY 0
	Activity Decreased #2	1		DAY 0
	Normal			DAY 6
	Normal			DAY 11
	Normal			DAY 13
	Rough Coat			DAY 1-DAY 5
	Rough Coat			DAY 7-DAY 10
	Rough Coat			DAY 12
	Rough Coat #1			DAY 0
	Rough Coat #2			DAY 0
	Rough Coat #3			DAY 0
	Scheduled Sacrifice			DAY 14
354	Activity Decreased #1	1		DAY 0
	Activity Decreased #2	1		DAY 0

Severity Codes

<u>Severity No.</u>	<u>Description</u>
1	Slight
2	Moderate
3	Severe

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105IP26
DAY 0-DAY 14

GROUP: 1-M
DOSE: 100 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
654 (contd.)	Activity Decreased #3	1		DAY 0
	Normal			DAY 6
	Normal			DAY 11
	Normal			DAY 13
	Rough Coat			DAY 1-DAY 5
	Rough Coat			DAY 7-DAY 10
	Rough Coat			DAY 12
	Rough Coat #1			DAY 0
	Rough Coat #2			DAY 0
	Rough Coat #3			DAY 0
	Scheduled Sacrifice			DAY 14
355	Activity Decreased #1	1		DAY 0
	Activity Decreased #2	1		DAY 0
	Activity Decreased #3	1		DAY 0
	Normal			DAY 4
	Normal			DAY 6-DAY 7
	Normal			DAY 11-DAY 13
	Rough Coat			DAY 1-DAY 3
	Rough Coat			DAY 5
	Rough Coat			DAY 8-DAY 10
	Rough Coat #1			DAY 0
	Rough Coat #2			DAY 0
	Rough Coat #3			DAY 0
	Scheduled Sacrifice			DAY 14

Severity Codes

<u>Severity No.</u>	<u>Description</u>
1	Slight
2	Moderate
3	Severe

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105IP26
DAY 0-DAY 14

GROUP: 2-M
DOSE: 120 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
361	Activity Decreased	1		DAY 2-DAY 3
	Comatose #1			DAY 0
	Activity Decreased #2	2		DAY 0
	Activity Decreased #3	2		DAY 0
	Normal			DAY 4
	Normal			DAY 13
	Rough Coat			DAY 1-DAY 3
	Rough Coat			DAY 5-DAY 12
	Rough Coat #3			DAY 0
	Scheduled Sacrifice			DAY 14
362	Activity Decreased	1		DAY 2-DAY 3
	Activity Decreased	1		DAY 5-DAY 6
	Activity Decreased #2	2		DAY 0
	Activity Decreased #3	2		DAY 0
	Animal Found Dead			DAY 6
	Hunched Posture			DAY 5-DAY 6
	Lethargic #1			DAY 0
	Rough Coat			DAY 1-DAY 6
	Rough Coat #2			DAY 0
	Rough Coat #3			DAY 0
363	Comatose #1			DAY 0
	Animal Found Dead			DAY 1
	Lethargic #2			DAY 0
	Lethargic #3			DAY 0
364	Activity Decreased	1		DAY 2-DAY 3
	Activity Decreased #2	2		DAY 0
	Activity Decreased #3	1		DAY 0
	Animal Found Dead			DAY 4
	Hunched Posture			DAY 3
	Lethargic #1			DAY 0
	Rough Coat			DAY 1-DAY 3
	Rough Coat #3			DAY 0
365	Activity Decreased	1		DAY 2-DAY 3

Severity Codes

<u>Severity No.</u>	<u>Description</u>
1	Slight
2	Moderate
3	Severe

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105IP26
DAY 0-DAY 14

GROUP: 3-M
DOSE: 140 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
371	Activity Decreased Comatose #1 Animal Found Dead Lethargic #2 Lethargic #3 Rough Coat	1		DAY 2-DAY 3 DAY 0 DAY 4 DAY 0 DAY 0 DAY 1-DAY 3
372	Comatose #1 Lethargic #2 Lethargic #3 Normal Normal Normal Rough Coat Rough Coat Rough Coat Scheduled Sacrifice			DAY 0 DAY 0 DAY 0 DAY 4 DAY 7-DAY 8 DAY 11-DAY 13 DAY 1-DAY 3 DAY 5-DAY 6 DAY 9-DAY 10 DAY 14
373	Activity Decreased Activity Decreased #2 Activity Decreased #3 Animal Found Dead Hunched Posture Lethargic #1 Rough Coat Rough Coat #2 Rough Coat #3	1 2 2		DAY 4 DAY 0 DAY 0 DAY 4 DAY 3 DAY 0 DAY 1-DAY 4 DAY 0 DAY 0
374	Comatose #1 Comatose #2 Comatose #3 Animal Found Dead Rough Coat			DAY 0 DAY 0 DAY 0 DAY 2 DAY 1
375	Comatose #1 Lethargic #2 Lethargic #3			DAY 0 DAY 0 DAY 0

Severity Codes

Severity No.	Description
1	Slight
2	Moderate
3	Severe

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105IP26
DAY 0-DAY 14

GROUP: 3-M
DOSE: 140 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
375 (contd.)	Normal			DAY 8
	Normal			DAY 11-DAY 13
	Rough Coat			DAY 1-DAY 7
	Rough Coat			DAY 9-DAY 10
	Scheduled Sacrifice			DAY 14

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105IP26
DAY 0-DAY 14

GROUP: 4-M
DOSE: 170 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
381	Activity Decreased	1		DAY 2-DAY 4
	Comatose #1			DAY 0
	Activity Decreased #3	1		DAY 0
	Animal Found Dead			DAY 4
	Lethargic #2			DAY 0
	Rough Coat			DAY 1-DAY 4
	Rough Coat #3			DAY 0
382	Comatose #1			DAY 0
	Comatose #2			DAY 0
	Comatose #3			DAY 0
	Animal Found Dead			DAY 1
383	Activity Decreased	1		DAY 5
	Activity Decreased	1		DAY 7-DAY 8
	Activity Decreased	3		DAY 9
	Ataxia	3		DAY 8-DAY 9
	Comatose #1			DAY 0
	Comatose #2			DAY 0
	Animal Found Dead			DAY 11
	Hunched Posture			DAY 5-DAY 9
	Lethargic #3			DAY 0
	Rough Coat			DAY 1-DAY 9
384	Comatose #1			DAY 0
	Hunched Posture			DAY 5
	Lethargic #2			DAY 0
	Lethargic #3			DAY 0
	Normal			DAY 4
	Normal			DAY 7
	Normal			DAY 13
	Rough Coat			DAY 1-DAY 3
	Rough Coat			DAY 5-DAY 6
	Rough Coat			DAY 8-DAY 12
	Scheduled Sacrifice			DAY 14
385	Activity Decreased	1		DAY 4-DAY 6

Severity Codes

Severity No.	Description
1	Slight
2	Moderate
3	Severe

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105IP26
DAY 0-DAY 14

GROUP: 4-M
DOSE: 170 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
385 (contd.)	Ataxia	1		DAY 3
	Comatose #1			DAY 0
	Comatose #2			DAY 0
	Animal Found Dead			DAY 6
	Hunched Posture			DAY 5-DAY 6
	Lethargic #3			DAY 0
	Rough Coat			DAY 1-DAY 6

Severity Codes

<u>Severity No.</u>	<u>Description</u>
1	Slight
2	Moderate
3	Severe

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105IP26
DAY 0-DAY 14

GROUP: 5-M
DOSE: 200 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
391	Comatose #1		DAY	0
	Comatose #2		DAY	0
	Comatose #3		DAY	0
	Animal Found Dead		DAY	1
392	Comatose #1		DAY	0
	Comatose #2		DAY	0
	Animal Found Dead		DAY	1
	Lethargic #3		DAY	0
393	Activity Decreased	1	DAY	2-DAY 3
	Comatose #1		DAY	0
	Comatose #2		DAY	0
	Animal Found Dead		DAY	4
	Lethargic #3		DAY	0
	Rough Coat		DAY	1-DAY 3
394	Activity Decreased	1	DAY	2-DAY 3
	Comatose #1		DAY	0
	Comatose #2		DAY	0
	Comatose #3		DAY	0
	Animal Found Dead		DAY	5
	Hunched Posture		DAY	3-DAY 4
	Rough Coat		DAY	1-DAY 4
395	Comatose #1		DAY	0
	Comatose #2		DAY	0
	Comatose #3		DAY	0
	Animal Found Dead		DAY	1

Severity Codes

<u>Severity No.</u>	<u>Description</u>
1	Slight
2	Moderate
3	Severe

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO24
DAY 0-DAY 14

GROUP: 1-F
DOSE: 10(mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
206	Normal		DAY 1	DAY 13
	Normal #1		DAY 0	
	Normal #2		DAY 0	
	Normal #3		DAY 0	
	Scheduled Sacrifice		DAY 14	
207	Normal		DAY 1	DAY 13
	Normal #1		DAY 0	
	Normal #2		DAY 0	
	Normal #3		DAY 0	
	Scheduled Sacrifice		DAY 14	
208	Normal		DAY 1	DAY 13
	Normal #1		DAY 0	
	Normal #2		DAY 0	
	Normal #3		DAY 0	
	Scheduled Sacrifice		DAY 14	
209	Normal		DAY 1	DAY 13
	Normal #1		DAY 0	
	Normal #2		DAY 0	
	Normal #3		DAY 0	
	Scheduled Sacrifice		DAY 14	
210	Normal		DAY 1	DAY 13
	Normal #1		DAY 0	
	Normal #2		DAY 0	
	Normal #3		DAY 0	
	Scheduled Sacrifice		DAY 14	

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO24
DAY 0-DAY 14

GROUP: 2-F
DOSE: 13 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
216	Normal			DAY 1-DAY 11
	Normal			DAY 13
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 12
	Scheduled Sacrifice			DAY 14
217	Normal			DAY 1-DAY 13
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Scheduled Sacrifice			DAY 14
218	Normal			DAY 1-DAY 13
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Scheduled Sacrifice			DAY 14
219	Normal			DAY 1-DAY 13
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Scheduled Sacrifice			DAY 14
220	Normal			DAY 1-DAY 13
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Scheduled Sacrifice			DAY 14

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO24
DAY 0-DAY 14

GROUP: 3-F
DOSE: 17(mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
226	Normal		DAY	1-DAY 3
	Normal		DAY	5
	Normal		DAY	9-DAY 11
	Normal		DAY	13
	Normal #1		DAY	0
	Normal #2		DAY	0
	Normal #3		DAY	0
	Rough Coat		DAY	4
	Rough Coat		DAY	6-DAY 8
	Rough Coat		DAY	12
	Scheduled Sacrifice		DAY	14
227	Normal		DAY	1-DAY 13
	Normal #1		DAY	0
	Normal #2		DAY	0
	Normal #3		DAY	0
	Scheduled Sacrifice		DAY	14
228	Normal		DAY	1-DAY 13
	Normal #1		DAY	0
	Normal #2		DAY	0
	Normal #3		DAY	0
	Scheduled Sacrifice		DAY	14
229	Normal		DAY	1-DAY 13
	Normal #1		DAY	0
	Normal #2		DAY	0
	Normal #3		DAY	0
	Scheduled Sacrifice		DAY	14
230	Dehydrated	1	DAY	10
	Hunched Posture		DAY	10
	Normal		DAY	1-DAY 9
	Normal		DAY	11
	Normal		DAY	13
	Normal #1		DAY	0
	Normal #2		DAY	0

Severity Codes

<u>Severity No.</u>	<u>Description</u>
1	Slight
2	Moderate
3	Severe

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO24
DAY 0-DAY 14

GROUP: 3-F
DOSE: 17(mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
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230 (contd.)

Normal #3
Rough Coat
Rough Coat
Scheduled Sacrifice

DAY 0
DAY 10
DAY 12
DAY 14

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO24
DAY 0-DAY 14

GROUP: 4-F
DOSE: 23 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
236	Ataxia Animal Found Dead Normal Normal #1 Normal #2 Normal #3	1		DAY 2 DAY 3 DAY 1 DAY 0 DAY 0 DAY 0
237	Normal Normal Normal Normal Normal #1 Normal #2 Normal #3 Rough Coat Rough Coat Rough Coat Scheduled Sacrifice			DAY 1-DAY 2 DAY 5 DAY 10-DAY 11 DAY 13 DAY 0 DAY 0 DAY 0 DAY 3-DAY 4 DAY 6-DAY 9 DAY 12 DAY 14
238	Hunched Posture Normal Normal Normal Normal #1 Normal #2 Normal #3 Rough Coat Rough Coat Rough Coat Scheduled Sacrifice			DAY 4-DAY 6 DAY 1-DAY 2 DAY 7 DAY 10-DAY 11 DAY 0 DAY 0 DAY 0 DAY 3-DAY 6 DAY 8-DAY 9 DAY 12-DAY 13 DAY 14
239	Animal Found Dead Normal Normal #1 Normal #2 Normal #3			DAY 3 DAY 1-DAY 2 DAY 0 DAY 0 DAY 0

Severity Codes

<u>Severity No.</u>	<u>Description</u>
1	Slight
2	Moderate
3	Severe

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO24
DAY 0-DAY 14

GROUP: 4-F
DOSE: 23 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
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240	Animal Found Dead			
	Normal			DAY 3
	Normal #1			DAY 1-DAY 2
	Normal #2			DAY 0
	Normal #3			DAY 0

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO24
DAY 0-DAY 14

GROUP: 5-F
DOSE: 30(mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
246	Ataxia	1		DAY 2
	Animal Found Dead			DAY 2
	Lethargic			DAY 2
	Normal			DAY 1
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
247	Ataxia	1		DAY 2
	Animal Found Dead			DAY 3
	Lethargic			DAY 2
	Normal			DAY 1
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
248	Animal Found Dead			DAY 1
	Normal			DAY 1
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
249	Animal Found Dead			DAY 3
	Normal			DAY 1-DAY 2
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
250	Animal Found Dead			DAY 2
	Normal			DAY 1
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0

Severity Codes

<u>Severity No.</u>	<u>Description</u>
1	Slight
2	Moderate
3	Severe

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105IP24
DAY 0-DAY 14

GROUP: 1-F
DOSE: 10 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
256	Normal		DAY	1-DAY 13
	Normal #1		DAY	0
	Normal #2		DAY	0
	Normal #3		DAY	0
	Scheduled Sacrifice		DAY	14
257	Normal		DAY	1-DAY 13
	Normal #1		DAY	0
	Normal #2		DAY	0
	Normal #3		DAY	0
	Scheduled Sacrifice		DAY	14
258	Normal		DAY	1-DAY 11
	Normal		DAY	13
	Normal #1		DAY	0
	Normal #2		DAY	0
	Normal #3		DAY	0
	Rough Coat		DAY	12
	Scheduled Sacrifice		DAY	14
259	Normal		DAY	1-DAY 13
	Normal #1		DAY	0
	Normal #2		DAY	0
	Normal #3		DAY	0
	Scheduled Sacrifice		DAY	14
260	Normal		DAY	1-DAY 11
	Normal		DAY	13
	Normal #1		DAY	0
	Normal #2		DAY	0
	Normal #3		DAY	0
	Rough Coat		DAY	12
	Scheduled Sacrifice		DAY	14

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105IP24
DAY 0-DAY 14

GROUP: 2-F
DOSE: 13(mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
266	Normal			DAY 1-DAY 13
	Normal #1			DAY 0
	Normal #2			DAY 0
				DAY 0
	Scheduled Sacrifice			DAY 14
267	Normal			DAY 1-DAY 11
	Normal			DAY 13
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 12
	Scheduled Sacrifice			DAY 14
268	Normal			DAY 1-DAY 11
	Normal			DAY 13
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 12
	Scheduled Sacrifice			DAY 14
269	Normal			DAY 1-DAY 13
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Scheduled Sacrifice			DAY 14
270	Normal			DAY 1-DAY 13
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Scheduled Sacrifice			DAY 14

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105IP24
DAY 0-DAY 14

GROUP: 3-F
DOSE: 17 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
276	Normal			DAY 1-DAY 11
	Normal			DAY 13
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 12
	Scheduled Sacrifice			DAY 14
277	Normal			DAY 1-DAY 11
	Normal			DAY 13
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 12
	Scheduled Sacrifice			DAY 14
278	Normal			DAY 1-DAY 11
	Normal			DAY 13
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 12
	Scheduled Sacrifice			DAY 14
279	Normal			DAY 1-DAY 11
	Normal			DAY 13
	Normal #1			DAY 0
	Normal #2			DAY 0
	Normal #3			DAY 0
	Rough Coat			DAY 12
	Scheduled Sacrifice			DAY 14
280	Normal			DAY 1
	Normal			DAY 6-DAY 11
	Normal			DAY 13
	Normal #1			DAY 0
	Normal #2			DAY 0

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105IP24
DAY 0-DAY 14

GROUP: 3-F
DOSE: 17(mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
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280 (contd.)	Normal #3			DAY 0
	Rough Coat			DAY 2-DAY 5
	Rough Coat			DAY 12
	Scheduled Sacrifice			DAY 14

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105IP24
DAY 0-DAY 14

GROUP: 4-F
DOSE: 23 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
286	Activity Decreased Animal Found Dead Normal #1 Normal #2 Normal #3 Rough Coat	1		DAY 2 DAY 3 DAY 0 DAY 0 DAY 0 DAY 1-DAY 2
287	Ataxia Animal Found Dead Normal Normal #1 Normal #2 Normal #3 Rough Coat	1		DAY 2 DAY 4 DAY 1 DAY 0 DAY 0 DAY 0 DAY 2-DAY 3
288	Activity Decreased Animal Found Dead Hunched Posture Normal #1 Normal #2 Normal #3 Rough Coat	1		DAY 1-DAY 2 DAY 3 DAY 2 DAY 0 DAY 0 DAY 0 DAY 2
289	Normal Normal Normal Normal Normal #1 Normal #2 Normal #3 Rough Coat Rough Coat Rough Coat Scheduled Sacrifice			DAY 1-DAY 6 DAY 9 DAY 11 DAY 13 DAY 0 DAY 0 DAY 0 DAY 7-DAY 8 DAY 10 DAY 12 DAY 14
290	Activity Decreased Animal Found Dead	1		DAY 1 DAY 3

Severity Codes

<u>Severity No.</u>	<u>Description</u>
1	Slight
2	Moderate
3	Severe

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105IP24
DAY 0-DAY 14

GROUP: 4-F
DOSE: 23 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
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290 (contd.)

Normal
Normal #1
Normal #2
Normal #3

DAY 2
DAY 0
DAY 0
DAY 0

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105IP24
DAY 0-DAY 14

GROUP: 5-F
DOSE: 30(mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
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296	Activity Decreased Animal Found Dead Normal Normal #1 Normal #2 Normal #3 Rough Coat	1		DAY 2 DAY 3 DAY 1 DAY 0 DAY 0 DAY 0 DAY 2
297	Animal Found Dead Normal #1 Normal #2 Normal #3 Rough Coat			DAY 3 DAY 0 DAY 0 DAY 0 DAY 1-DAY 2
298	Animal Found Dead Normal Normal #1 Normal #2 Normal #3 Rough Coat			DAY 3 DAY 1 DAY 0 DAY 0 DAY 0 DAY 2
299	Ataxia Animal Found Dead Normal Normal #1 Normal #2 Normal #3 Rough Coat	1		DAY 2 DAY 3 DAY 1 DAY 0 DAY 0 DAY 0 DAY 2
300	Activity Decreased Comatose Animal Found Dead Normal #1 Normal #2 Normal #3 Rough Coat	1		DAY 1 DAY 2 DAY 3 DAY 0 DAY 0 DAY 0 DAY 1-DAY 2

Severity Codes

Severity No.	Description
1	Slight
2	Moderate
3	Severe

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO26
DAY 0-DAY 14

GROUP: 1-F
DOSE: 1100 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
306	Animal Found Dead			DAY 1
	Lethargic #1			DAY 0
	Lethargic #2			DAY 0
	Lethargic #3			DAY 0
307	Activity Decreased #1	1		DAY 0
	Hunched Posture			DAY 5
	Normal			DAY 7
	Normal			DAY 11-DAY 13
	Rough Coat			DAY 1-DAY 6
	Rough Coat			DAY 8-DAY 10
	Rough Coat #2			DAY 0
	Rough Coat #3			DAY 0
	Scheduled Sacrifice			DAY 14
308	Comatose #1			DAY 0
	Comatose #2			DAY 0
	Comatose #3			DAY 0
	Animal Found Dead			DAY 1
309	Activity Decreased #1	1		DAY 0
	Activity Decreased #2	1		DAY 0
	Activity Decreased #3	1		DAY 0
	Animal Found Dead			DAY 1
	Lethargic			DAY 1
	Rough Coat			DAY 1
	Rough Coat #1			DAY 0
	Rough Coat #2			DAY 0
	Rough Coat #3			DAY 0
310	Comatose #2			DAY 0
	Animal Found Dead			DAY 1
	Lethargic #1			DAY 0
	Lethargic #3			DAY 0

Severity Codes

<u>Severity No.</u>	<u>Description</u>
1	Slight
2	Moderate
3	Severe

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO26
DAY 0-DAY 14

GROUP: 2-F
DOSE: 1300 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
316	Comatose #2			DAY 0
	Comatose #3			DAY 0
	Animal Found Dead			DAY 1
	Lethargic #1			DAY 0
317	Activity Decreased #1	1		DAY 0
	Activity Decreased #2	1		DAY 0
	Hunched Posture			DAY 5-DAY 6
	Hunched Posture #3			DAY 0
	Normal			DAY 4
	Normal			DAY 7
	Normal			DAY 11-DAY 13
	Rough Coat			DAY 1-DAY 3
	Rough Coat			DAY 5-DAY 6
	Rough Coat			DAY 8-DAY 10
	Rough Coat #1			DAY 0
	Rough Coat #2			DAY 0
	Rough Coat #3			DAY 0
	Scheduled Sacrifice			DAY 14
318	Activity Decreased #1	1		DAY 0
	Activity Decreased #2	2		DAY 0
	Activity Decreased #3	1		DAY 0
	Animal Found Dead			DAY 1
	Rough Coat #1			DAY 0
	Rough Coat #2			DAY 0
319	Activity Decreased #1	1		DAY 0
	Activity Decreased #2	2		DAY 0
	Activity Decreased #3	1		DAY 0
	Animal Found Dead			DAY 1
	Hunched Posture #3			DAY 0
	Rough Coat #1			DAY 0
	Rough Coat #2			DAY 0
	Rough Coat #3			DAY 0
320	Animal Found Dead			DAY 1
	Lethargic #1			DAY 0
	Lethargic #2			DAY 0
	Lethargic #3			DAY 0

Severity Codes

<u>Severity No.</u>	<u>Description</u>
1	Slight
2	Moderate
3	Severe

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO26
DAY 0-DAY 14

GROUP: 3-F
DOSE: 1500 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
326	Activity Decreased #2	2		DAY 0
	Activity Decreased #3	1		DAY 0
	Animal Found Dead			DAY 1
	Lethargic #1			DAY 0
	Rough Coat #2			DAY 0
	Rough Coat #3			DAY 0
327	Animal Found Dead			DAY 1
	Lethargic #1			DAY 0
	Lethargic #2			DAY 0
	Lethargic #3			DAY 0
328	Comatose #1			DAY 0
	Comatose #2			DAY 0
	Comatose #3			DAY 0
	Animal Found Dead			DAY 1
329	Activity Decreased #2	2		DAY 0
	Activity Decreased #3	1		DAY 0
	Animal Found Dead			DAY 2
	Lethargic			DAY 1
	Lethargic #1			DAY 0
	Rough Coat			DAY 1
	Rough Coat #2			DAY 0
	Rough Coat #3			DAY 0
330	Activity Decreased	1		DAY 5-DAY 6
	Activity Decreased #1	1		DAY 0
	Activity Decreased #2	1		DAY 0
	Hunched Posture			DAY 6
	Hunched Posture			DAY 9
	Normal			DAY 11-DAY 13
	Rough Coat			DAY 1-DAY 10
	Rough Coat #2			DAY 0
	Rough Coat #3			DAY 0
	Scheduled Sacrifice			DAY 14

Severity Codes

Severity No.	Description
1	Slight
2	Moderate
3	Severe

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO26
DAY 0-DAY 14

GROUP: 4-F
DOSE: 1750 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
336	Activity Decreased #1	2		DAY 0
	Activity Decreased #2	3		DAY 0
	Activity Decreased #3	3		DAY 0
	Animal Found Dead			DAY 1
	Rough Coat #3			DAY 0
337	Comatose #1			DAY 0
	Comatose #2			DAY 0
	Comatose #3			DAY 0
	Animal Found Dead			DAY 1
338	Comatose #1			DAY 0
	Comatose #2			DAY 0
	Animal Found Dead			DAY 1
	Lethargic #3			DAY 0
339	Comatose #1			DAY 0
	Comatose #2			DAY 0
	Comatose #3			DAY 0
	Animal Found Dead			DAY 1
340	Activity Decreased #1	1		DAY 0
	Animal Found Dead			DAY 2
	Lethargic			DAY 1
	Lethargic #2			DAY 0
	Lethargic #3			DAY 0
	Rough Coat			DAY 1
	Rough Coat #1			DAY 0
	Rough Coat #2			DAY 0
	Rough Coat #3			DAY 0

Severity Codes

<u>Severity No.</u>	<u>Description</u>
1	Slight
2	Moderate
3	Severe

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO26
DAY 0-DAY 14

GROUP: 5-F
DOSE: 2000 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
346	Comatose #2 Activity Decreased #1 Animal Found Dead Lethargic #3	1		DAY 0 DAY 0 DAY 1 DAY 0
347	Activity Decreased #1 Activity Decreased #2 Activity Decreased #3 Animal Found Dead Rough Coat Rough Coat #2 Rough Coat #3	1 1 1		DAY 0 DAY 0 DAY 0 DAY 2 DAY 1-DAY 2 DAY 0 DAY 0
348	Comatose #2 Activity Decreased #3 Animal Found Dead Lethargic #1 Rough Coat #3	2		DAY 0 DAY 0 DAY 1 DAY 0 DAY 0
349	Comatose #2 Comatose #3 Animal Found Dead Lethargic #1			DAY 0 DAY 0 DAY 1 DAY 0
350	Comatose #2 Animal Found Dead Lethargic #1			DAY 0 DAY 0 DAY 0

Severity Codes

<u>Severity No.</u>	<u>Description</u>
1	Slight
2	Moderate
3	Severe

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO26
DAY 0-DAY 14

GROUP: 6-F
DOSE: 800 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
406	Comatose			DAY 1
	Activity Decreased #1	2		DAY 0
	Activity Decreased #2	2		DAY 0
	Activity Decreased #3	2		DAY 0
	Animal Found Dead			DAY 2
	Rough Coat			DAY 1
	Rough Coat #1			DAY 0
	Rough Coat #2			DAY 0
	Rough Coat #3			DAY 0
407	Activity Decreased #3	3		DAY 0
	Animal Found Dead			DAY 1
	Lethargic #1			DAY 0
	Lethargic #2			DAY 0
	Rough Coat #3			DAY 0
408	Animal Found Dead			DAY 1
	Lethargic #1			DAY 0
	Lethargic #2			DAY 0
	Lethargic #3			DAY 0
409	Animal Found Dead			DAY 1
	Lethargic #1			DAY 0
	Lethargic #2			DAY 0
	Lethargic #3			DAY 0
410	Activity Decreased #2	2		DAY 0
	Activity Decreased #3	2		DAY 0
	Animal Found Dead			DAY 3
	Lethargic #1			DAY 0
	Rough Coat			DAY 1-DAY 2
	Rough Coat #2			DAY 0
	Rough Coat #3			DAY 0

Severity Codes

<u>Severity No.</u>	<u>Description</u>
1	Slight
2	Moderate
3	Severe

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO6A
DAY 0-DAY 14

GROUP: 1-F
DOSE: 0 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
636	Normal			DAY 1-DAY 8
	Normal			DAY 11-DAY 13
	Normal 1			DAY 0
	Normal 2			DAY 0
	Normal 3			DAY 0
	Rough Coat			DAY 9-DAY 10
	Scheduled Sacrifice			DAY 14
637	Normal			DAY 1-DAY 8
	Normal			DAY 11-DAY 12
	Normal 1			DAY 0
	Normal 2			DAY 0
	Normal 3			DAY 0
	Rough Coat			DAY 9-DAY 10
	Rough Coat			DAY 13
	Scheduled Sacrifice			DAY 14
638	Normal			DAY 1-DAY 13
	Normal 1			DAY 0
	Normal 2			DAY 0
	Normal 3			DAY 0
	Scheduled Sacrifice			DAY 14
639	Normal			DAY 1-DAY 9
	Normal			DAY 11-DAY 13
	Normal 1			DAY 0
	Normal 2			DAY 0
	Normal 3			DAY 0
	Rough Coat			DAY 10
	Scheduled Sacrifice			DAY 14
640	Normal			DAY 1-DAY 13
	Normal 1			DAY 0
	Normal 2			DAY 0
	Normal 3			DAY 0
	Scheduled Sacrifice			DAY 14

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO6A
DAY 0-DAY 14

GROUP: 2-F
DOSE: 0 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
616	Decreased Activity 1	1		DAY 0
	Decreased Activity 2	1		DAY 0
	Animal Found Dead			DAY 0
	Hunched Posture 1			DAY 0
	Hunched Posture 2			DAY 0
	Lethargic 3			DAY 0
	Rough Coat 1			DAY 0
	Rough Coat 2			DAY 0
	Rough Coat 3			DAY 0
617	Decreased Activity 1	1		DAY 0
	Hunched Posture 3			DAY 0
	Normal			DAY 1-DAY 3
	Normal			DAY 5
	Normal			DAY 8-DAY 11
	Rough Coat			DAY 4
	Rough Coat			DAY 6-DAY 7
	Rough Coat			DAY 12-DAY 13
	Rough Coat 1			DAY 0
	Rough Coat 2			DAY 0
	Rough Coat 3			DAY 0
	Scheduled Sacrifice			DAY 14
618	Decreased Activity 1	1		DAY 0
	Decreased Activity 2	2		DAY 0
	Decreased Activity 3	2		DAY 0
	Animal Found Dead			DAY 1
	Hunched Posture 1			DAY 0
	Hunched Posture 2			DAY 0
	Hunched Posture 3			DAY 0
	Rough Coat 1			DAY 0
	Rough Coat 2			DAY 0
	Rough Coat 3			DAY 0
619	Hunched Posture 1			DAY 0
	Normal			DAY 1-DAY 5
	Normal			DAY 7-DAY 12

Severity Codes

<u>Severity No.</u>	<u>Description</u>
1	Slight
2	Moderate
3	Severe

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO6A
DAY 0-DAY 14

GROUP: 2-F
DOSE: 0 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
619 (contd.)	Rough Coat			DAY 6
	Rough Coat			DAY 13
	Rough Coat 1			DAY 0
	Rough Coat 2			DAY 0
	Rough Coat 3			DAY 0
	Scheduled Sacrifice			DAY 14
620	Decreased Activity 1	1		DAY 0
	Hunched Posture 1			DAY 0
	Normal			DAY 1-DAY 13
	Rough Coat 1			DAY 0
	Rough Coat 2			DAY 0
	Rough Coat 3			DAY 0
	Scheduled Sacrifice			DAY 14

Severity Codes

<u>Severity No.</u>	<u>Description</u>
1	Slight
2	Moderate
3	Severe

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO6A
DAY 0-DAY 14

GROUP: 3-F
DOSE: 800 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
626	Decreased Activity 1 Hunched Posture Normal Normal Rough Coat Rough Coat Rough Coat 1 Rough Coat 2 Rough Coat 3 Scheduled Sacrifice	1 		DAY 0 DAY 5 DAY 1 DAY 6-DAY 7 DAY 2-DAY 5 DAY 8-DAY 13 DAY 0 DAY 0 DAY 0 DAY 14
627	Decreased Activity 1 Decreased Activity 2 Decreased Activity 3 Hunched Posture Normal Normal Rough Coat Rough Coat Rough Coat 1 Rough Coat 2 Rough Coat 3 Scheduled Sacrifice	1 1 2 		DAY 0 DAY 0 DAY 0 DAY 3 DAY 6 DAY 8-DAY 13 DAY 1-DAY 5 DAY 7 DAY 0 DAY 0 DAY 0 DAY 14
628	Animal Found Dead Labored Breathing 2 Labored Breathing 3 Lethargic 1 Lethargic 2 Lethargic 3 Rough Coat 2 Rough Coat 3	 		DAY 1 DAY 0 DAY 0 DAY 0 DAY 0 DAY 0 DAY 0 DAY 0
629	Hunched Posture Normal Normal Rough Coat	 		DAY 3-DAY 4 DAY 1-DAY 2 DAY 5-DAY 13 DAY 3-DAY 4

Severity Codes

<u>Severity No.</u>	<u>Description</u>
1	Slight
2	Moderate
3	Severe

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105P06A
DAY 0-DAY 14

GROUP: 3-F
DOSE: 800 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
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629 (contd.)	Rough Coat 1			DAY 0
	Rough Coat 2			DAY 0
	Rough Coat 3			DAY 0
	Scheduled Sacrifice			DAY 14
630	Decreased Activity 1	1		DAY 0
	Decreased Activity 2	1		DAY 0
	Decreased Activity 3	2		DAY 0
	Animal Found Dead			DAY 1
	Hunched Posture 2			DAY 0
	Hunched Posture 3			DAY 0
	Rough Coat 1			DAY 0
	Rough Coat 2			DAY 0
	Rough Coat 3			DAY 0

Severity Codes

<u>Severity No.</u>	<u>Description</u>
1	Slight
2	Moderate
3	Severe

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO6A
DAY 0-DAY 14

GROUP: 4-F
DOSE: 1000(mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
606	Blue Feet 1			DAY 0
	Decreased Activity 1	1		DAY 0
	Decreased Activity 3	1		DAY 0
	Hunched Posture			DAY 2-DAY 9
	Hunched Posture			DAY 12-DAY 13
	Hunched Posture 1			DAY 0
	Hunched Posture 2			DAY 0
	Hunched Posture 3			DAY 0
	Rough Coat			DAY 1-DAY 13
	Rough Coat 1			DAY 0
	Rough Coat 2			DAY 0
	Rough Coat 3			DAY 0
	Scheduled Sacrifice			DAY 14
607	Blue Feet 1			DAY 0
	Decreased Activity 1	1		DAY 0
	Decreased Activity 2	1		DAY 0
	Decreased Activity 3	2		DAY 0
	Animal Found Dead			DAY 1
	Hunched Posture 1			DAY 0
	Hunched Posture 2			DAY 0
	Hunched Posture 3			DAY 0
	Rough Coat 1			DAY 0
	Rough Coat 2			DAY 0
	Rough Coat 3			DAY 0
608	Hunched Posture			DAY 4
	Hunched Posture 2			DAY 0
	Hunched Posture 3			DAY 0
	Normal			DAY 2
	Normal			DAY 6-DAY 13
	Rough Coat			DAY 1
	Rough Coat			DAY 3-DAY 5
	Rough Coat 1			DAY 0
	Rough Coat 2			DAY 0
	Rough Coat 3			DAY 0
	Scheduled Sacrifice			DAY 14

Severity Codes

Severity No.	Description
1	Slight
2	Moderate
3	Severe

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105PO6A
DAY 0-DAY 14

GROUP: 4-F
DOSE: 1000 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
609	Animal Found Dead			DAY 0
610	Blue Feet 1			DAY 0
	Blue Feet 2			DAY 0
	Decreased Activity 1	1		DAY 0
	Decreased Activity 2	1		DAY 0
	Hunched Posture			DAY 3-DAY 4
	Hunched Posture 1			DAY 0
	Hunched Posture 2			DAY 0
	Hunched Posture 3			DAY 0
	Normal			DAY 1-DAY 2
	Normal			DAY 5-DAY 12
	Rough Coat			DAY 3-DAY 4
	Rough Coat			DAY 13
	Rough Coat 1			DAY 0
	Rough Coat 2			DAY 0
	Rough Coat 3			DAY 0
	Scheduled Sacrifice			DAY 14

Severity Codes

Severity No.	Description
1	Slight
2	Moderate
3	Severe

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105IP26
DAY 0-DAY 14

GROUP: 1-F
DOSE: 100 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
356	Activity Decreased #2	1		DAY 0
	Activity Decreased #3	1		DAY 0
	Lethargic #1			DAY 0
	Normal			DAY 4
	Normal			DAY 6
	Normal			DAY 11-DAY 13
	Rough Coat			DAY 1-DAY 3
	Rough Coat			DAY 5
	Rough Coat			DAY 7-DAY 10
	Rough Coat #2			DAY 0
	Rough Coat #3			DAY 0
	Scheduled Sacrifice			DAY 14
357	Activity Decreased #1	1		DAY 0
	Activity Decreased #2	1		DAY 0
	Activity Decreased #3	1		DAY 0
	Normal			DAY 4
	Normal			DAY 6-DAY 8
	Normal			DAY 11-DAY 13
	Rough Coat			DAY 1-DAY 3
	Rough Coat			DAY 5
	Rough Coat			DAY 9-DAY 10
	Rough Coat #3			DAY 0
	Scheduled Sacrifice			DAY 14
358	Activity Decreased #1	1		DAY 0
	Activity Decreased #2	1		DAY 0
	Activity Decreased #3	1		DAY 0
	Normal			DAY 4
	Normal			DAY 6-DAY 7
	Normal			DAY 11-DAY 13
	Rough Coat			DAY 1-DAY 3
	Rough Coat			DAY 5
	Rough Coat			DAY 8-DAY 10
	Rough Coat #1			DAY 0
	Rough Coat #3			DAY 0
	Scheduled Sacrifice			DAY 14

Severity Codes

<u>Severity No.</u>	<u>Description</u>
1	Slight
2	Moderate
3	Severe

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105IP26
DAY 0-DAY 14

GROUP: 1-F
DOSE: 100 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
359	Activity Decreased #1	1		DAY 0
	Activity Decreased #2	1		DAY 0
	Activity Decreased #3	1		DAY 0
	Normal			DAY 2-DAY 4
	Normal			DAY 6
	Normal			DAY 11-DAY 13
	Rough Coat			DAY 1
	Rough Coat			DAY 5
	Rough Coat			DAY 7-DAY 10
	Rough Coat #3			DAY 0
	Scheduled Sacrifice			DAY 14
360	Activity Decreased #1	1		DAY 0
	Activity Decreased #2	1		DAY 0
	Activity Decreased #3	1		DAY 0
	Normal			DAY 2-DAY 13
	Rough Coat			DAY 1
	Rough Coat #3			DAY 0
	Scheduled Sacrifice			DAY 14

Severity Codes

<u>Severity No.</u>	<u>Description</u>
1	Slight
2	Moderate
3	Severe

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105IP26
DAY 0-DAY 14

GROUP: 2-F
DOSE: 120 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
366	Comatose #1 Hunched Posture Lethargic #2 Lethargic #3 Normal Rough Coat Rough Coat #3 Scheduled Sacrifice			DAY 0 DAY 2-DAY 3 DAY 0 DAY 0 DAY 13 DAY 1-DAY 12 DAY 0 DAY 14
367	Comatose #2 Lethargic #1 Lethargic #3 Normal Normal Rough Coat Rough Coat Rough Coat #3 Scheduled Sacrifice			DAY 0 DAY 0 DAY 0 DAY 6-DAY 8 DAY 13 DAY 1-DAY 5 DAY 9-DAY 12 DAY 0 DAY 14
368	Activity Decreased #1 Activity Decreased #3 Lethargic #2 Normal Normal Normal Rough Coat Rough Coat Rough Coat Rough Coat #3 Scheduled Sacrifice	2 2		DAY 0 DAY 0 DAY 0 DAY 2-DAY 4 DAY 6-DAY 8 DAY 13 DAY 1 DAY 5 DAY 9-DAY 12 DAY 0 DAY 14
369	Comatose #1 Activity Decreased #3 Lethargic #2 Normal Normal Rough Coat Rough Coat Rough Coat #3 Scheduled Sacrifice	2		DAY 0 DAY 0 DAY 0 DAY 3-DAY 4 DAY 6-DAY 13 DAY 1-DAY 2 DAY 5 DAY 0 DAY 14

Severity Codes

<u>Severity No.</u>	<u>Description</u>
1	Slight
2	Moderate
3	Severe

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105IP26
DAY 0-DAY 14

GROUP: 2-F
DOSE: 120 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
370	Activity Decreased #1	2		DAY 0
	Activity Decreased #2	1		DAY 0
	Activity Decreased #3	1		DAY 0
	Normal			DAY 2-DAY 4
	Normal			DAY 6-DAY 13
	Rough Coat			DAY 1
	Rough Coat			DAY 5
	Rough Coat #1			DAY 0
	Rough Coat #2			DAY 0
	Rough Coat #3			DAY 0
	Scheduled Sacrifice			DAY 14

Severity Codes

<u>Severity No.</u>	<u>Description</u>
1	Slight
2	Moderate
3	Severe

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105IP26
DAY 0-DAY 14

GROUP: 3-F
DOSE: 140 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
376	Activity Decreased Comatose #1 Animal Found Dead Lethargic #2 Lethargic #3 Rough Coat	1		DAY 2-DAY 4 DAY 0 DAY 4 DAY 0 DAY 0 DAY 1-DAY 4
377	Comatose #1 Animal Found Dead Lethargic Lethargic #2 Lethargic #3 Rough Coat			DAY 0 DAY 2 DAY 1 DAY 0 DAY 0 DAY 1
378	Activity Decreased #3 Lethargic #1 Lethargic #2 Normal Normal Normal Rough Coat Rough Coat Rough Coat Rough Coat #2 Rough Coat #3 Scheduled Sacrifice	2		DAY 0 DAY 0 DAY 0 DAY 2-DAY 4 DAY 6 DAY 11-DAY 13 DAY 1 DAY 5 DAY 7-DAY 10 DAY 0 DAY 0 DAY 14
379	Comatose #1 Comatose #2 Lethargic #3 Normal Normal Rough Coat Rough Coat Scheduled Sacrifice			DAY 0 DAY 0 DAY 0 DAY 4 DAY 6-DAY 13 DAY 1-DAY 3 DAY 5 DAY 14
380	Comatose #1			DAY 0

Severity Codes

<u>Severity No.</u>	<u>Description</u>
1	Slight
2	Moderate
3	Severe

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105IP26
DAY 0-DAY 14

GROUP: 3-F
DOSE: 140 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
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380 (contd.)	Lethargic #2			DAY 0
	Lethargic #3			DAY 0
	Normal			DAY 3-DAY 4
	Normal			DAY 6
	Normal			DAY 8-DAY 13
	Rough Coat			DAY 1-DAY 2
	Rough Coat			DAY 5
	Rough Coat			DAY 7
	Rough Coat #2			DAY 0
	Rough Coat #3			DAY 0
	Scheduled Sacrifice			DAY 14

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105IP26
DAY 0-DAY 14

GROUP: 4-F
DOSE: 170 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
386	Comatose #1			DAY 0
	Comatose #2			DAY 0
	Comatose #3			DAY 0
	Animal Found Dead			DAY 2
	Lethargic			DAY 1
	Rough Coat			DAY 1
387	Comatose #1			DAY 0
	Comatose #2			DAY 0
	Lethargic			DAY 1
	Lethargic #3			DAY 0
	Normal			DAY 4
	Normal			DAY 7
	Normal			DAY 11-DAY 12
	Rough Coat			DAY 1-DAY 3
	Rough Coat			DAY 5-DAY 6
	Rough Coat			DAY 8-DAY 10
	Rough Coat			DAY 13
	Scheduled Sacrifice			DAY 14
388	Comatose #1			DAY 0
	Comatose #2			DAY 0
	Lethargic #3			DAY 0
	Rough Coat			DAY 1-DAY 13
	Rough Coat #3			DAY 0
	Scheduled Sacrifice			DAY 14
389	Comatose #1			DAY 0
	Comatose #2			DAY 0
	Lethargic #3			DAY 0
	Normal			DAY 4
	Normal			DAY 6-DAY 7
	Normal			DAY 11-DAY 13
	Rough Coat			DAY 1-DAY 3
	Rough Coat			DAY 5
	Rough Coat			DAY 8-DAY 10
	Rough Coat #3			DAY 0
	Scheduled Sacrifice			DAY 14

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105IP26
DAY 0-DAY 14

GROUP: 4-F
DOSE: 170 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
390	Comatose #1			DAY 0
	Comatose #2			DAY 0
	Activity Decreased #3	1		DAY 0
	Normal			DAY 4
	Normal			DAY 6-DAY 7
	Normal			DAY 13
	Rough Coat			DAY 1-DAY 3
	Rough Coat			DAY 5
	Rough Coat			DAY 8-DAY 12
	Rough Coat #3			DAY 0
	Scheduled Sacrifice			DAY 14

Severity Codes

<u>Severity No.</u>	<u>Description</u>
1	Slight
2	Moderate
3	Severe

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL OBSERVATIONS

STUDY: 105IP26
DAY 0-DAY 14

GROUP: 5-F
DOSE: 200 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
396	Comatose #1			DAY 0
	Comatose #2			DAY 0
	Comatose #3			DAY 0
	Hunched Posture			DAY 1-DAY 3
	Hunched Posture			DAY 6
	Normal			DAY 4
	Normal			DAY 7
	Normal			DAY 13
	Rough Coat			DAY 1-DAY 3
	Rough Coat			DAY 5-DAY 6
	Rough Coat			DAY 8-DAY 12
	Scheduled Sacrifice			DAY 14
397	Comatose #1			DAY 0
	Animal Found Dead			DAY 0
398	Comatose #1			DAY 0
	Hunched Posture			DAY 1-DAY 2
	Hunched Posture			DAY 6
	Lethargic #2			DAY 0
	Lethargic #3			DAY 0
	Normal			DAY 4
	Normal			DAY 11-DAY 13
	Rough Coat			DAY 1-DAY 3
	Rough Coat			DAY 5-DAY 10
	Scheduled Sacrifice			DAY 14
399	Comatose #1			DAY 0
	Comatose #2			DAY 0
	Comatose #3			DAY 0
	Animal Found Dead			DAY 2
	Hunched Posture			DAY 1
	Rough Coat			DAY 1
400	Comatose #1			DAY 0
	Animal Found Dead			DAY 0

APPENDIX 4

Individual Body Weights and Body Weight Gains

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105PO24

GROUP: 1-M

SEX: MALE

DOSE: 10 (mg/kg)

ANIMAL # DAY -3 DAY 0 DAY 7 DAY 14

201	26.0	27.4	28.8	29.4
202	24.6	26.2	28.6	30.8
203	26.7	27.8	28.4	30.4
204	27.2	28.2	29.7	32.2
205	24.9	26.6	28.1	30.0

MEAN	25.9	27.2	28.7	30.6
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S.D.	1.12	0.83	0.61	1.05
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N	5	5	5	5
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--: Data Unavailable

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105PO24

GROUP: 2-M

SEX: MALE

DOSE: 13 (mg/kg)

ANIMAL # DAY -3 DAY 0 DAY 7 DAY 14

211	28.4	30.3	31.8	34.1
212	24.0	25.7	28.6	30.7
213	26.8	27.7	30.7	32.9
214	25.8	27.7	29.6	32.3
215	25.2	27.2	29.0	29.0

MEAN	26.0	27.7	29.9	31.8
S.D.	1.66	1.66	1.31	1.99
N	5	5	5	5

--: Data Unavailable

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105PO24

GROUP: 3-M

SEX: MALE

DOSE: 17 (mg/kg)

ANIMAL # DAY -3 DAY 0 DAY 7 DAY 14

221	27.0	28.6	30.4	32.2
222	24.6	25.5	25.2	26.7
223	27.3	28.7	30.3	32.9
224	26.4	27.8	29.7	31.1
225	25.3	25.8	28.5	30.1

MEAN	26.1	27.3	28.8	30.6
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S.D.	1.14	1.53	2.16	2.43
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N	5	5	5	5
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--: Data Unavailable

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105PO24

GROUP: 4-M

SEX: MALE

DOSE: 23 (mg/kg)

ANIMAL # DAY -3 DAY 0 DAY 7 DAY 14

231	27.1	27.4	30.4	31.4
232	23.7	25.1	c	c
233	26.9	28.2	c	c
234	26.3	27.8	30.7	33.4
235	25.7	26.6	29.7	32.6

MEAN	25.9	27.0	30.3	32.5
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S.D.	1.37	1.23	0.51	1.01
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N	5	5	3	3
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--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105PO24

GROUP: 5-M

SEX: MALE

DOSE: 30 (mg/kg)

ANIMAL # DAY -3 DAY 0 DAY 7 DAY 14

241	28.0	30.3	c	c
242	24.2	25.1	c	c
243	26.5	28.9	c	c
244	25.2	26.5	c	c
245	26.2	27.8	c	c

MEAN	26.0	27.7	--	--
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S.D.	1.43	2.03	--	--
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N	5	5	0	0
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--: Data Unavailable c: Animal Found Dead

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105IP24

GROUP: 1-M

SEX: MALE

DOSE: 10 (mg/kg)

ANIMAL # DAY -3 DAY 0 DAY 7 DAY 14

251	26.7	27.9	28.8	30.6
252	24.2	25.5	27.0	30.7
253	24.7	25.9	26.7	27.5
254	28.0	30.3	31.1	34.6
255	25.9	28.6	29.2	31.8

MEAN	25.9	27.6	28.6	31.0
S.D.	1.53	1.98	1.79	2.55
N	5	5	5	5

--: Data Unavailable

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105IP24

GROUP: 2-M

SEX: MALE

DOSE: 13 (mg/kg)

ANIMAL # DAY -3 DAY 0 DAY 7 DAY 14

261	25.7	27.6	29.4	31.1
262	24.0	25.1	25.7	26.6
263	26.9	28.0	29.8	31.6
264	26.4	27.4	29.0	31.7
265	28.2	28.8	31.2	32.9

MEAN	26.2	27.4	29.0	30.8
S.D.	1.55	1.38	2.03	2.43
N	5	5	5	5

--: Data Unavailable

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105IP24

GROUP: 3-M

SEX: MALE

DOSE: 17 (mg/kg)

ANIMAL # DAY -3 DAY 0 DAY 7 DAY 14

271	25.2	27.5	29.1	31.1
272	24.7	27.2	28.9	30.8
273	26.8	28.4	29.1	32.7
274	28.4	30.0	28.7	32.1
275	26.1	27.8	29.3	31.6

MEAN	26.2	28.2	29.0	31.7
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S.D.	1.45	1.11	0.23	0.76
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N	5	5	5	5
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--: Data Unavailable

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105IP24

GROUP: 4-M

SEX: MALE

DOSE: 23 (mg/kg)

ANIMAL # DAY -3 DAY 0 DAY 7 DAY 14

281	27.8	29.9	c	c
282	23.7	24.8	c	c
283	25.7	27.2	27.0	29.6
284	27.0	28.8	c	c
285	25.9	26.5	c	c

MEAN 26.0 27.4 27.0 29.6

S.D. 1.55 1.99 -- --

N 5 5 1 1

--: Data Unavailable c: Animal Found Dead

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105IP24

GROUP: 5-M

SEX: MALE

DOSE: 30 (mg/kg)

ANIMAL # DAY -3 DAY 0 DAY 7 DAY 14

291	28.0	28.7	c	c
292	25.5	27.2	c	c
293	24.0	26.0	c	c
294	26.2	27.2	c	c
295	26.7	27.8	c	c

MEAN	26.1	27.4	--	--
S.D.	1.48	0.99	--	--
N	5	5	0	0

--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105PO26

GROUP: 1-M

SEX: MALE

DOSE: 1100 (mg/kg)

ANIMAL # PRETEST DAY 0 DAY 7 DAY 14

301	28.2	29.7	30.7	31.8
302	29.0	29.7	c	c
303	30.3	30.9	c	c
304	27.8	29.1	30.0	30.9
305	26.1	27.5	28.6	29.1

MEAN	28.3	29.4	29.8	30.6
S.D.	1.55	1.24	1.07	1.37
N	5	5	3	3

--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105PO26

GROUP: 2-M

SEX: MALE

DOSE: 1300 (mg/kg)

ANIMAL # PRETEST DAY 0 DAY 7 DAY 14

311	29.3	30.4	24.3	31.4
312	25.3	25.4	c	c
313	28.0	29.5	c	c
314	31.3	32.5	c	c
315	27.7	28.6	30.6	31.0

MEAN	28.3	29.3	27.5	31.2
S.D.	2.20	2.61	4.45	0.28
N	5	5	2	2

--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105PO26

GROUP: 3-M

SEX: MALE

DOSE: 1500 (mg/kg)

ANIMAL # PRETEST DAY 0 DAY 7 DAY 14

321	27.6	28.6	25.9	30.8
322	26.7	28.0	c	c
323	27.8	29.2	c	c
324	28.9	30.0	c	c
325	30.5	32.1	c	c

MEAN	28.3	29.6	25.9	30.8
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S.D.	1.46	1.59	--	--
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N	5	5	1	1
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--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105PO26

GROUP: 4-M

SEX: MALE

DOSE: 1750 (mg/kg)

ANIMAL # PRETEST DAY 0 DAY 7 DAY 14

331	29.3	30.3	c	c
332	25.0	25.2	c	c
333	27.0	28.8	c	c
334	31.1	31.4	c	c
335	28.1	29.7	c	c

MEAN	28.1	29.1	--	--
S.D.	2.31	2.37	--	--
N	5	5	0	0

--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105PO26

GROUP: 5-M

SEX: MALE

DOSE: 2000 (mg/kg)

ANIMAL # PRETEST DAY 0 DAY 7 DAY 14

341	30.5	31.0	c	c
342	26.5	28.0	c	c
343	27.1	28.8	26.6	29.2
344	29.4	31.7	c	c
345	27.9	28.1	c	c

MEAN 28.3 29.5 26.6 29.2

S.D. 1.65 1.72 -- --

N 5 5 1 1

--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105PO26

GROUP: 6-M

SEX: MALE

DOSE: 800 (mg/kg)

ANIMAL # PRETEST DAY 0 DAY 7 DAY 14

401	22.7	24.6	c	c
402	26.5	31.1	c	c
403	25.7	25.7	26.6	27.6
404	26.3	27.9	c	c
405	27.6	29.4	c	c

MEAN 25.8 27.7 26.6 27.6

S.D. 1.84 2.65 -- --

N 5 5 1 1

--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105PO6A

GROUP: 1-M

SEX: MALE

DOSE: 0 (mg/kg)

ANIMAL # DAY -2 DAY 0 DAY 7 DAY 14

631	28.1	28.8	32.6	32.2
632	28.2	29.1	31.7	32.8
633	26.8	27.3	31.8	30.8
634	29.5	28.3	33.6	23.1
635	30.2	30.2	c	c

MEAN 28.6 28.7 32.4 29.7

S.D. 1.32 1.06 0.88 4.50

N 5 5 4 4

--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105PO6A

GROUP: 2-M

SEX: MALE

DOSE: 0 (mg/kg)

ANIMAL # DAY -2 DAY 0 DAY 7 DAY 14

611	27.4	28.9	32.0	31.6
612	30.0	31.1	34.5	34.0
613	28.3	29.1	31.3	32.3
614	28.6	28.8	31.6	32.7
615	30.7	31.7	c	c

MEAN	29.0	29.9	32.4	32.7
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S.D.	1.33	1.37	1.46	1.01
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N	5	5	4	4
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--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105PO6A

GROUP: 3-M

SEX: MALE

DOSE: 800 (mg/kg)

ANIMAL # DAY -2 DAY 0 DAY 7 DAY 14

621	28.4	29.7	32.2	31.0
622	30.5	31.4	c	c
623	27.5	28.7	c	c
624	26.3	26.9	28.1	28.0
625	29.7	30.4	c	c

MEAN	28.5	29.4	30.2	29.5
S.D.	1.68	1.72	2.90	2.12
N	5	5	2	2

--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105P06A

GROUP: 4-M

SEX: MALE

DOSE: 1000 (mg/kg)

ANIMAL # DAY -2 DAY 0 DAY 7 DAY 14

601	27.5	28.2	30.7	30.6
602	26.1	27.1	28.8	29.9
603	29.0	29.3	c	c
604	30.4	31.3	33.6	33.9
605	28.3	29.9	32.5	31.5

MEAN 28.3 29.2 31.4 31.5

S.D. 1.61 1.61 2.11 1.74

N 5 5 4 4

--: Data Unavailable c: Animal Found Dead

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105IP26

GROUP: 1-M

SEX: MALE

DOSE: 100 (mg/kg)

ANIMAL # DAY -3 DAY 0 DAY 7 DAY 14

351	27.8	28.7	28.0	30.1
352	29.8	30.4	c	c
353	28.7	29.8	31.8	33.3
354	26.2	29.3	29.3	31.2
355	27.8	28.1	27.3	24.8

MEAN	28.1	29.3	29.1	29.9
S.D.	1.33	0.90	1.98	3.62
N	5	5	4	4

--: Data Unavailable c: Animal Found Dead

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105IP26

GROUP: 2-M

SEX: MALE

DOSE: 120 (mg/kg)

ANIMAL # DAY -3 DAY 0 DAY 7 DAY 14

361	30.2	31.5	31.7	33.3
362	26.4	27.8	c	c
363	27.6	28.1	c	c
364	28.7	30.0	c	c
365	28.8	29.5	c	c

MEAN	28.3	29.4	31.7	33.3
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S.D.	1.42	1.50	--	--
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N	5	5	1	1
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--: Data Unavailable c: Animal Found Dead

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105IP26

GROUP: 3-M

SEX: MALE

DOSE: 140 (mg/kg)

ANIMAL # DAY -3 DAY 0 DAY 7 DAY 14

371	28.7	29.1	c	c
372	29.4	29.9	31.0	33.3
373	27.2	28.3	c	c
374	24.9	26.4	c	c
375	30.2	31.5	32.4	33.2

MEAN	28.1	29.0	31.7	33.3
S.D.	2.09	1.89	0.99	0.07
N	5	5	2	2

--: Data Unavailable c: Animal Found Dead

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105IP26

GROUP: 4-M

SEX: MALE

DOSE: 170 (mg/kg)

ANIMAL # DAY -3 DAY 0 DAY 7 DAY 14

381	27.6	28.2	c	c
382	28.6	29.7	c	c
383	26.9	28.3	20.6	c
384	28.8	30.3	31.1	32.0
385	29.5	30.5	c	c

MEAN	28.3	29.4	25.9	32.0
------	------	------	------	------

S.D.	1.03	1.09	7.42	--
------	------	------	------	----

N	5	5	2	1
---	---	---	---	---

--: Data Unavailable c: Animal Found Dead

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105IP26

GROUP: 5-M

SEX: MALE

DOSE: 200 (mg/kg)

ANIMAL # DAY -3 DAY 0 DAY 7 DAY 14

391	28.8	29.4	c	c
392	26.2	27.0	c	c
393	28.3	29.1	c	c
394	27.4	28.3	c	c
395	31.1	31.3	c	c

MEAN 28.4 29.0 -- --

S.D. 1.82 1.58 -- --

N 5 5 0 0

--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105PO24

GROUP: 1-M

SEX: MALE

DOSE: 10 (mg/kg)

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

201	1.4	0.6	2.0
202	2.4	2.2	4.6
203	0.6	2.0	2.6
204	1.5	2.5	4.0
205	1.5	1.9	3.4

MEAN	1.5	1.8	3.3
S.D.	0.64	0.73	1.04
N	5	5	5

--: Data Unavailable b: Scheduled Sacrifice

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105PO24

GROUP: 2-M
DOSE: 13 (mg/kg)

SEX: MALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

211	1.5	2.3	3.8
212	2.9	2.1	5.0
213	3.0	2.2	5.2
214	1.9	2.7	4.6
215	1.8	0.0	1.8

MEAN	2.2	1.9	4.1
S.D.	0.68	1.06	1.38
N	5	5	5

--: Data Unavailable b: Scheduled Sacrifice

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105PO24

GROUP: 3-M
DOSE: 17 (mg/kg)

SEX: MALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

221	1.8	1.8	3.6
222	-0.3	1.5	1.2
223	1.6	2.6	4.2
224	1.9	1.4	3.3
225	2.7	1.6	4.3

MEAN	1.5	1.8	3.3
S.D.	1.11	0.48	1.26
N	5	5	5

--: Data Unavailable b: Scheduled Sacrifice

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105PO24

GROUP: 4-M

SEX: MALE

DOSE: 23 (mg/kg)

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

231	3.0	1.0	4.0
232	c	c	--
233	c	c	--
234	2.9	2.7	5.6
235	3.1	2.9	6.0

MEAN	3.0	2.2	5.2
S.D.	0.10	1.04	1.06
N	3	3	3

--: Data Unavailable

b: Scheduled Sacrifice

c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105PO24

GROUP: 5-M

SEX: MALE

DOSE: 30(mg/kg)

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
241	c	c	--
242	c	c	--
243	c	c	--
244	c	c	--
245	c	c	--
MEAN	--	--	--
S.D.	--	--	--
N	0	0	0

--: Data Unavailable

c: Animal Found Dead

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105IP24

GROUP: 1-M

SEX: MALE

DOSE: 10(mg/kg)

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
251	0.9	1.8	2.7
252	1.5	3.7	5.2
253	0.8	0.8	1.6
254	0.8	3.5	4.3
255	0.6	2.6	3.2

MEAN	0.9	2.5	3.4
S.D.	0.34	1.21	1.40
N	5	5	5

--: Data Unavailable b: Scheduled Sacrifice

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105IP24

GROUP: 2-M

SEX: MALE

DOSE: 13 (mg/kg)

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

261	1.8	1.7	3.5
262	0.6	0.9	1.5
263	1.8	1.8	3.6
264	1.6	2.7	4.3
265	2.4	1.7	4.1

MEAN	1.6	1.8	3.4
S.D.	0.65	0.64	1.11
N	5	5	5

--: Data Unavailable b: Scheduled Sacrifice

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105IP24

GROUP: 3-M

SEX: MALE

DOSE: 17(mg/kg)

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

271	1.6	2.0	3.6
272	1.7	1.9	3.6
273	0.7	3.6	4.3
274	-1.3	3.4	2.1
275	1.5	2.3	3.8

MEAN	0.8	2.6	3.5
S.D.	1.26	0.80	0.82
N	5	5	5

--: Data Unavailable b: Scheduled Sacrifice

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105IP24

GROUP: 4-M

SEX: MALE

DOSE: 23 (mg/kg)

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

281	c	c	--
282	c	c	--
283	-0.2	2.6	2.4
284	c	c	--
285	c	c	--

MEAN	-0.2	2.6	2.4
S.D.	--	--	--
N	1	1	1

--: Data Unavailable

b: Scheduled Sacrifice

c: Animal Found Dead

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105IP24

GROUP: 5-M

SEX: MALE

DOSE: 30(mg/kg)

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
291	c	c	--
292	c	c	--
293	c	c	--
294	c	c	--
295	c	c	--
MEAN	--	--	--
S.D.	--	--	--
N	0	0	0

--: Data Unavailable

c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105PO26

GROUP: 1-M

SEX: MALE

DOSE: 1100 (mg/kg)

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	------------

301	1.0	1.1	2.1
302	c	c	--
303	c	c	--
304	0.9	0.9	1.8
305	1.1	0.5	1.6

MEAN	1.0	0.8	1.8
------	-----	-----	-----

S.D.	0.10	0.31	0.25
------	------	------	------

N	3	3	3
---	---	---	---

--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105P026

GROUP: 2-M

SEX: MALE

DOSE: 1300 (mg/kg)

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
311	-6.1	7.1	1.0
312	c	c	--
313	c	c	--
314	c	c	--
315	2.0	0.4	2.4
MEAN	-2.1	3.8	1.7
S.D.	5.73	4.74	0.99
N	2	2	2

--: Data Unavailable

c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105PO26

GROUP: 3-M
DOSE: 1500 (mg/kg)

SEX: MALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
321	-2.7	4.9	2.2
322	c	c	--
323	c	c	--
324	c	c	--
325	c	c	--
MEAN	-2.7	4.9	2.2
S.D.	--	--	--
N	1	1	1

--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105PO26

GROUP: 4-M
DOSE: 1750 (mg/kg)

SEX: MALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

331	c	c	--
332	c	c	--
333	c	c	--
334	c	c	--
335	c	c	--

MEAN	--	--	--
S.D.	--	--	--
N	0	0	0

--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105PO26

GROUP: 5-M
DOSE: 2000 (mg/kg)

SEX: MALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

341	c	c	--
342	c	c	--
343	-2.2	2.6	0.4
344	c	c	--
345	c	c	--

MEAN	-2.2	2.6	0.4
S.D.	--	--	--
N	1	1	1

--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105PO26

GROUP: 6-M
DOSE: 800 (mg/kg)

SEX: MALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

401	c	c	--
402	c	c	--
403	0.9	1.0	1.9
404	c	c	--
405	c	c	--

MEAN	0.9	1.0	1.9
S.D.	--	--	--
N	1	1	1

--: Data Unavailable

b: Scheduled Sacrifice

c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105P06A

GROUP: 1-M
DOSE: 0 (mg/kg)

SEX: MALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

631	3.8	-0.4	3.4
632	2.6	1.1	3.7
633	4.5	-1.0	3.5
634	5.3	-10.5	-5.2
635	c	c	--

MEAN	4.1	-2.7	1.4
S.D.	1.14	5.27	4.37
N	4	4	4

--: Data Unavailable

b: Scheduled Sacrifice

c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105PO6A

GROUP: 2-M
DOSE: 0 (mg/kg)

SEX: MALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
611	3.1	-0.4	2.7
612	3.4	-0.5	2.9
613	2.2	1.0	3.2
614	2.8	1.1	3.9
615	c	c	--
MEAN	2.9	0.3	3.2
S.D.	0.51	0.87	0.53
N	4	4	4

--: Data Unavailable

b: Scheduled Sacrifice

c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105P06A

GROUP: 3-M
DOSE: 800 (mg/kg)

SEX: MALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

621	2.5	-1.2	1.3
622	c	c	--
623	c	c	--
624	1.2	-0.1	1.1
625	c	c	--

MEAN	1.9	-0.7	1.2
S.D.	0.92	0.78	0.14
N	2	2	2

--: Data Unavailable

b: Scheduled Sacrifice

c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105PO6A

GROUP: 4-M
DOSE: 1000 (mg/kg)

SEX: MALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

601	2.5	-0.1	2.4
602	1.7	1.1	2.8
603	c	c	--
604	2.3	0.3	2.6
605	2.6	-1.0	1.6

MEAN	2.3	0.1	2.4
S.D.	0.40	0.87	0.53
N	4	4	4

--: Data Unavailable

b: Scheduled Sacrifice

c: Animal Found Dead

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105IP26

GROUP: 1-M
DOSE: 100 (mg/kg)

SEX: MALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
351	-0.7	2.1	1.4
352	c	c	--
353	2.0	1.5	3.5
354	0.0	1.9	1.9
355	-0.8	-2.5	-3.3
MEAN	0.1	0.8	0.9
S.D.	1.30	2.18	2.92
N	4	4	4

--: Data Unavailable

b: Scheduled Sacrifice

c: Animal Found Dead

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105IP26

GROUP: 2-M
DOSE: 120 (mg/kg)

SEX: MALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

361	0.2	1.6	1.8
362	c	c	--
363	c	c	--
364	c	c	--
365	c	c	--

MEAN	0.2	1.6	1.8
S.D.	--	--	--
N	1	1	1

--: Data Unavailable

b: Scheduled Sacrifice

c: Animal Found Dead

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105IP26

GROUP: 3-M
DOSE: 140 (mg/kg)

SEX: MALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

371	c	c	--
372	1.1	2.3	3.4
373	c	c	--
374	c	c	--
375	0.9	0.8	1.7

MEAN	1.0	1.6	2.6
S.D.	0.14	1.06	1.20
N	2	2	2

--: Data Unavailable

b: Scheduled Sacrifice

c: Animal Found Dead

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105IP26

GROUP: 4-M
DOSE: 170 (mg/kg)

SEX: MALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

381	c	c	--
382	c	c	--
383	-7.7	c	--
384	0.8	0.9	1.7
385	c	c	--

MEAN	-3.5	0.9	1.7
------	------	-----	-----

S.D.	6.01	--	--
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N	2	1	1
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--: Data Unavailable

b: Scheduled Sacrifice

c: Animal Found Dead

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105IP26

GROUP: 5-M
DOSE: 200 (mg/kg)

SEX: MALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

391	c	c	--
392	c	c	--
393	c	c	--
394	c	c	--
395	c	c	--

MEAN	--	--	--
S.D.	--	--	--
N	0	0	0

--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105PO24

GROUP: 1-F

SEX: FEMALE

DOSE: 10 (mg/kg)

ANIMAL # DAY -3 DAY 0 DAY 7 DAY 14

206	22.7	23.9	25.7	26.1
207	23.5	23.3	25.5	25.4
208	20.9	22.3	24.6	24.7
209	22.2	23.6	23.9	26.5
210	24.5	25.8	27.0	29.4

MEAN	22.8	23.8	25.3	26.4
------	------	------	------	------

S.D.	1.36	1.28	1.18	1.80
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N	5	5	5	5
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--: Data Unavailable

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105PO24

GROUP: 2-F

SEX: FEMALE

DOSE: 13 (mg/kg)

ANIMAL # DAY -3 DAY 0 DAY 7 DAY 14

216	24.5	26.3	26.5	29.0
217	21.3	21.2	24.3	26.7
218	23.9	24.7	27.2	28.5
219	23.1	23.7	25.7	26.5
220	22.4	24.0	23.4	23.9

MEAN	23.0	24.0	25.4	26.9
------	------	------	------	------

S.D.	1.26	1.85	1.56	2.01
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N	5	5	5	5
---	---	---	---	---

--: Data Unavailable

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105PO24

GROUP: 3-F

SEX: FEMALE

DOSE: 17 (mg/kg)

ANIMAL # DAY -3 DAY 0 DAY 7 DAY 14

226	23.2	24.2	26.2	28.9
227	25.1	25.9	26.6	29.5
228	22.6	22.5	23.6	25.0
229	21.9	22.9	24.5	26.2
230	23.8	24.0	18.2	29.3

MEAN	23.3	23.9	23.8	27.8
S.D.	1.22	1.33	3.37	2.05
N	5	5	5	5

--: Data Unavailable

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105PO24

GROUP: 4-F
DOSE: 23 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY -3	DAY 0	DAY 7	DAY 14
236	22.4	22.3	c	c
237	21.1	22.3	23.9	25.5
238	24.2	23.5	22.1	24.5
239	25.3	25.3	c	c
240	23.2	22.3	c	c
MEAN	23.2	23.1	23.0	25.0
S.D.	1.62	1.31	1.27	0.71
N	5	5	2	2

--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105PO24

GROUP: 5-F

SEX: FEMALE

DOSE: 30 (mg/kg)

ANIMAL # DAY -3 DAY 0 DAY 7 DAY 14

246	25.0	25.3	c	c
247	22.9	23.9	c	c
248	22.3	22.5	c	c
249	23.5	23.6	c	c
250	22.1	23.8	c	c

MEAN	23.2	23.8	--	--
------	------	------	----	----

S.D.	1.17	1.00	--	--
------	------	------	----	----

N	5	5	0	0
---	---	---	---	---

--: Data Unavailable c: Animal Found Dead

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105IP24

GROUP: 1-F

SEX: FEMALE

DOSE: 10 (mg/kg)

ANIMAL # DAY -3 DAY 0 DAY 7 DAY 14

256	22.9	23.2	24.9	26.1
257	24.9	25.5	26.7	25.9
258	22.6	24.6	28.9	29.2
259	23.5	25.0	26.3	27.6
260	21.2	23.2	22.9	25.8

MEAN	23.0	24.3	25.9	26.9
S.D.	1.35	1.05	2.22	1.47
N	5	5	5	5

--: Data Unavailable

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105IP24

GROUP: 2-F

SEX: FEMALE

DOSE: 13 (mg/kg)

ANIMAL # DAY -3 DAY 0 DAY 7 DAY 14

266	24.3	25.7	26.2	28.3
267	21.8	23.7	24.5	28.3
268	22.4	23.9	25.0	27.6
269	23.1	23.2	24.9	25.9
270	24.3	25.5	26.0	27.6

MEAN	23.2	24.4	25.3	27.5
S.D.	1.12	1.13	0.74	0.98
N	5	5	5	5

--: Data Unavailable

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105IP24

GROUP: 3-F

SEX: FEMALE

DOSE: 17 (mg/kg)

ANIMAL # DAY -3 DAY 0 DAY 7 DAY 14

276	22.6	24.4	24.3	25.2
277	25.3	26.7	28.0	30.4
278	23.9	24.8	25.5	27.3
279	21.6	25.2	25.7	28.3
280	23.3	23.1	23.1	25.5

MEAN	23.3	24.8	25.3	27.3
S.D.	1.39	1.31	1.83	2.14
N	5	5	5	5

--: Data Unavailable

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105IP24

GROUP: 4-F

SEX: FEMALE

DOSE: 23 (mg/kg)

ANIMAL # DAY -3 DAY 0 DAY 7 DAY 14

286	22.2	23.8	c	c
287	24.6	26.1	c	c
288	23.5	25.2	c	c
289	23.3	24.2	25.8	26.5
290	22.0	22.5	c	c

MEAN 23.1 24.4 25.8 26.5

S.D. 1.06 1.37 -- --

N 5 5 1 1

--: Data Unavailable c: Animal Found Dead

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105IP24

GROUP: 5-F

SEX: FEMALE

DOSE: 30 (mg/kg)

ANIMAL # DAY -3 DAY 0 DAY 7 DAY 14

296	25.4	26.1	c	c
297	24.2	26.3	c	c
298	23.2	23.7	c	c
299	20.3	21.9	c	c
300	22.3	22.8	c	c

MEAN	23.1	24.2	--	--
S.D.	1.94	1.97	--	--
N	5	5	0	0

--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105PO26

GROUP: 1-F

SEX: FEMALE

DOSE: 1100 (mg/kg)

ANIMAL # PRETEST DAY 0 DAY 7 DAY 14

306	26.2	26.5	c	c
307	25.1	24.1	25.3	26.9
308	23.6	23.7	c	c
309	25.7	26.7	c	c
310	22.5	22.4	c	c

MEAN 24.6 24.7 25.3 26.9

S.D. 1.54 1.86 -- --

N 5 5 1 1

--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105PO26

GROUP: 2-F

SEX: FEMALE

DOSE: 1300 (mg/kg)

ANIMAL # PRETEST DAY 0 DAY 7 DAY 14

316	23.9	24.3	c	c
317	23.2	22.0	19.5	25.0
318	26.0	26.0	c	c
319	27.7	27.2	c	c
320	25.3	25.9	c	c

MEAN 25.2 25.1 19.5 25.0

S.D. 1.77 2.01 -- --

N 5 5 1 1

--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105PO26

GROUP: 3-F

SEX: FEMALE

DOSE: 1500 (mg/kg)

ANIMAL # PRETEST DAY 0 DAY 7 DAY 14

326	24.5	24.9	c	c
327	23.4	24.5	c	c
328	23.6	24.2	c	c
329	26.1	25.5	c	c
330	25.8	25.0	19.8	26.4

MEAN	24.7	24.8	19.8	26.4
S.D.	1.24	0.50	--	--
N	5	5	1	1

--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105PO26

GROUP: 4-F

SEX: FEMALE

DOSE: 1750 (mg/kg)

ANIMAL # PRETEST DAY 0 DAY 7 DAY 14

336	24.9	25.2	c	c
337	24.1	24.4	c	c
338	23.0	24.3	c	c
339	25.5	26.7	c	c
340	26.5	26.5	c	c

MEAN	24.8	25.4	--	--
S.D.	1.33	1.13	--	--
N	5	5	0	0

--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105PO26

GROUP: 5-F
DOSE: 2000 (mg/kg)

SEX: FEMALE

ANIMAL # PRETEST DAY 0 DAY 7 DAY 14

346	25.2	25.5	c	c
347	26.5	27.5	c	c
348	25.4	25.8	c	c
349	22.1	23.2	c	c
350	23.8	21.9	c	c

MEAN	24.6	24.8	--	--
S.D.	1.70	2.22	--	--
N	5	5	0	0

--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105P026

GROUP: 6-F

SEX: FEMALE

DOSE: 800 (mg/kg)

ANIMAL # PRETEST DAY 0 DAY 7 DAY 14

406	18.6	21.8	c	c
407	24.4	24.7	c	c
408	23.4	23.6	c	c
409	20.8	21.9	c	c
410	25.8	25.8	c	c

MEAN	22.6	23.6	--	--
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S.D.	2.89	1.74	--	--
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N	5	5	0	0
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--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105P06A

GROUP: 1-F
DOSE: 0 (mg/kg)

SEX: FEMALE

ANIMAL # DAY -2 DAY 0 DAY 7 DAY 14

636	23.3	23.6	26.6	25.2
637	25.3	24.7	27.9	28.6
638	22.4	23.1	24.6	25.1
639	22.2	23.4	25.8	25.5
640	23.7	23.5	25.0	16.9

MEAN	23.4	23.7	26.0	24.3
S.D.	1.24	0.61	1.32	4.36
N	5	5	5	5

--: Data Unavailable

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105PO6A

GROUP: 2-F
DOSE: 0 (mg/kg)

SEX: FEMALE

ANIMAL # DAY -2 DAY 0 DAY 7 DAY 14

616	24.2	25.3	c	c
617	21.8	22.5	23.5	23.6
618	23.2	23.9	c	c
619	23.6	23.6	25.1	27.0
620	24.5	24.4	24.5	26.2

MEAN	23.5	23.9	24.4	25.6
S.D.	1.06	1.03	0.81	1.78
N	5	5	3	3

--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105PO6A

GROUP: 3-F

SEX: FEMALE

DOSE: 800 (mg/kg)

ANIMAL # DAY -2 DAY 0 DAY 7 DAY 14

626	23.6	24.5	26.8	27.2
627	24.3	25.1	28.0	27.7
628	21.3	22.8	c	c
629	22.4	23.6	24.2	25.9
630	24.4	24.7	c	c

MEAN 23.2 24.1 26.3 26.9

S.D. 1.33 0.93 1.94 0.93

N 5 5 3 3

--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105PO6A

GROUP: 4-F

SEX: FEMALE

DOSE: 1000 (mg/kg)

ANIMAL # DAY -2 DAY 0 DAY 7 DAY 14

606	24.0	24.3	20.4	25.8
607	25.4	25.9	c	c
608	22.4	23.4	25.4	25.6
609	23.3	24.7	c	c
610	21.1	22.8	25.1	15.9

MEAN 23.2 24.2 23.6 22.4

S.D. 1.62 1.20 2.80 5.66

N 5 5 3 3

--: Data Unavailable c: Animal Found Dead

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105IP26

GROUP: 1-F

SEX: FEMALE

DOSE: 100 (mg/kg)

ANIMAL # DAY -3 DAY 0 DAY 7 DAY 14

356	23.8	25.0	25.9	26.4
357	24.9	25.5	26.1	27.1
358	26.2	26.2	26.7	27.1
359	25.8	25.5	27.4	27.3
360	22.5	22.2	23.1	23.7

MEAN 24.6 24.9 25.8 26.3

S.D. 1.51 1.56 1.64 1.50

N 5 5 5 5

--: Data Unavailable

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105IP26

GROUP: 2-F

SEX: FEMALE

DOSE: 120 (mg/kg)

ANIMAL # DAY -3 DAY 0 DAY 7 DAY 14

366	25.5	24.5	26.5	27.5
367	23.6	24.2	24.0	25.3
368	26.3	27.2	28.5	27.9
369	23.7	22.6	24.2	25.3
370	24.9	24.9	27.0	26.8

MEAN	24.8	24.7	26.0	26.6
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S.D.	1.16	1.66	1.92	1.22
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N	5	5	5	5
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--: Data Unavailable

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105IP26

GROUP: 3-F

SEX: FEMALE

DOSE: 140 (mg/kg)

ANIMAL # DAY -3 DAY 0 DAY 7 DAY 14

376	24.9	25.1	c	c
377	23.3	23.9	c	c
378	24.0	24.2	25.5	27.6
379	25.9	26.5	28.1	28.9
380	27.0	27.6	27.2	28.2

MEAN	25.0	25.5	26.9	28.2
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S.D.	1.48	1.57	1.32	0.65
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N	5	5	3	3
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--: Data Unavailable c: Animal Found Dead

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105IP26

GROUP: 4-F

SEX: FEMALE

DOSE: 170 (mg/kg)

ANIMAL # DAY -3 DAY 0 DAY 7 DAY 14

386	23.6	23.4	c	c
387	24.5	24.5	25.4	25.7
388	25.3	24.9	26.8	27.2
389	23.4	23.9	27.1	28.0
390	27.5	28.6	28.3	29.5

MEAN 24.9 25.1 26.9 27.6

S.D. 1.66 2.06 1.19 1.59

N 5 5 4 4

--: Data Unavailable c: Animal Found Dead

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 105IP26

GROUP: 5-F

SEX: FEMALE

DOSE: 200 (mg/kg)

ANIMAL # DAY -3 DAY 0 DAY 7 DAY 14

396	26.2	27.8	26.4	29.4
397	22.8	22.8	c	c
398	25.9	26.5	27.7	28.9
399	24.3	23.9	c	c
400	23.6	24.1	c	c

MEAN 24.6 25.0 27.1 29.2

S.D. 1.46 2.06 0.92 0.35

N 5 5 2 2

--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105PO24

GROUP: 1-F
DOSE: 10(mg/kg)

SEX: FEMALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

206	1.8	0.4	2.2
207	2.2	-0.1	2.1
208	2.3	0.1	2.4
209	0.3	2.6	2.9
210	1.2	2.4	3.6

MEAN	1.6	1.1	2.6
S.D.	0.83	1.31	0.62
N	5	5	5

--: Data Unavailable b: Scheduled Sacrifice

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105PO24

GROUP: 2-F
DOSE: 13(mg/kg)

SEX: FEMALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

216	0.2	2.5	2.7
217	3.1	2.4	5.5
218	2.5	1.3	3.8
219	2.0	0.8	2.8
220	-0.6	0.5	-0.1

MEAN	1.4	1.5	2.9
S.D.	1.57	0.91	2.04
N	5	5	5

--: Data Unavailable b: Scheduled Sacrifice

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105PO24

GROUP: 3-F
DOSE: 17 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

226	2.0	2.7	4.7
227	0.7	2.9	3.6
228	1.1	1.4	2.5
229	1.6	1.7	3.3
230	-5.8	11.1	5.3

MEAN	-0.1	4.0	3.9
S.D.	3.24	4.04	1.12
N	5	5	5

--: Data Unavailable b: Scheduled Sacrifice

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105PO24

GROUP: 4-F
DOSE: 23 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

236	c	c	--
237	1.6	1.6	3.2
238	-1.4	2.4	1.0
239	c	c	--
240	c	c	--

MEAN	0.1	2.0	2.1
S.D.	2.12	0.57	1.56
N	2	2	2

--: Data Unavailable

b: Scheduled Sacrifice

c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR242511 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105PO24

GROUP: 5-F
DOSE: 30 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
246	c	c	--
247	c	c	--
248	c	c	--
249	c	c	--
250	c	c	--
MEAN	--	--	--
S.D.	--	--	--
N	0	0	0

--: Data Unavailable c: Animal Found Dead

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105IP24

GROUP: 1-F
DOSE: 10 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
256	1.7	1.2	2.9
257	1.2	-0.8	0.4
258	4.3	0.3	4.6
259	1.3	1.3	2.6
260	-0.3	2.9	2.6
MEAN	1.6	1.0	2.6
S.D.	1.67	1.37	1.49
N	5	5	5

--: Data Unavailable b: Scheduled Sacrifice

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105IP24

GROUP: 2-F
DOSE: 13 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
266	0.5	2.1	2.6
267	0.8	3.8	4.6
268	1.1	2.6	3.7
269	1.7	1.0	2.7
270	0.5	1.6	2.1
MEAN	0.9	2.2	3.1
S.D.	0.50	1.06	1.00
N	5	5	5

--: Data Unavailable b: Scheduled Sacrifice

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105IP24

GROUP: 3-F
DOSE: 17 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
276	-0.1	0.9	0.8
277	1.3	2.4	3.7
278	0.7	1.8	2.5
279	0.5	2.6	3.1
280	0.0	2.4	2.4
MEAN	0.5	2.0	2.5
S.D.	0.57	0.69	1.08
N	5	5	5

--: Data Unavailable b: Scheduled Sacrifice

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105IP24

GROUP: 4-F
DOSE: 23 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

286	c	c	--
287	c	c	--
288	c	c	--
289	1.6	0.7	2.3
290	c	c	--

MEAN	1.6	0.7	2.3
------	-----	-----	-----

S.D.	--	--	--
------	----	----	----

N	1	1	1
---	---	---	---

--: Data Unavailable

b: Scheduled Sacrifice

c: Animal Found Dead

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR242511 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105IP24

GROUP: 5-F
DOSE: 30 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
296	c	c	--
297	c	c	--
298	c	c	--
299	c	c	--
300	c	c	--
MEAN	--	--	--
S.D.	--	--	--
N	0	0	0

--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105PO26

GROUP: 1-F
DOSE: 1100 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
306	c	c	--
307	1.2	1.6	2.8
308	c	c	--
309	c	c	--
310	c	c	--
MEAN	1.2	1.6	2.8
S.D.	--	--	--
N	1	1	1

--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105PO26

GROUP: 2-F
DOSE: 1300 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
316	c	c	--
317	-2.5	5.5	3.0
318	c	c	--
319	c	c	--
320	c	c	--
MEAN	-2.5	5.5	3.0
S.D.	--	--	--
N	1	1	1

--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105PO26

GROUP: 3-F
DOSE: 1500 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

326	c	c	--
327	c	c	--
328	c	c	--
329	c	c	--
330	-5.2	6.6	1.4

MEAN	-5.2	6.6	1.4
------	------	-----	-----

S.D.	--	--	--
------	----	----	----

N	1	1	1
---	---	---	---

--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105PO26

GROUP: 4-F
DOSE: 1750 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

336	c	c	--
337	c	c	--
338	c	c	--
339	c	c	--
340	c	c	--

MEAN	--	--	--
------	----	----	----

S.D.	--	--	--
------	----	----	----

N	0	0	0
---	---	---	---

--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105PO26

GROUP: 5-F
DOSE: 2000 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

346	c	c	--
347	c	c	--
348	c	c	--
349	c	c	--
350	c	c	--

MEAN	--	--	--
S.D.	--	--	--
N	0	0	0

--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105PO26

GROUP: 6-F
DOSE: 800 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
406	c	c	--
407	c	c	--
408	c	c	--
409	c	c	--
410	c	c	--
MEAN	--	--	--
S.D.	--	--	--
N	0	0	0

--: Data Unavailable c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105P06A

GROUP: 1-F
DOSE: 0 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

636	3.0	-1.4	1.6
637	3.2	0.7	3.9
638	1.5	0.5	2.0
639	2.4	-0.3	2.1
640	1.5	-8.1	-6.6

MEAN	2.3	-1.7	0.6
S.D.	0.80	3.66	4.12
N	5	5	5

--: Data Unavailable b: Scheduled Sacrifice

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105PO6A

GROUP: 2-F
DOSE: 0 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

616	c	c	--
617	1.0	0.1	1.1
618	c	c	--
619	1.5	1.9	3.4
620	0.1	1.7	1.8

MEAN	0.9	1.2	2.1
S.D.	0.71	0.99	1.18
N	3	3	3

--: Data Unavailable

b: Scheduled Sacrifice

c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105PO6A

GROUP: 3-F
DOSE: 800 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

626	2.3	0.4	2.7
627	2.9	-0.3	2.6
628	c	c	--
629	0.6	1.7	2.3
630	c	c	--

MEAN	1.9	0.6	2.5
S.D.	1.19	1.01	0.21
N	3	3	3

--: Data Unavailable

b: Scheduled Sacrifice

c: Animal Found Dead

ACUTE ORAL TOXICITY STUDY OF
WR269410 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105PO6A

GROUP: 4-F
DOSE: 1000 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

606	-3.9	5.4	1.5
607	c	c	--
608	2.0	0.2	2.2
609	c	c	--
610	2.3	-9.2	-6.9

MEAN	0.1	-1.2	-1.1
S.D.	3.50	7.40	5.06
N	3	3	3

--: Data Unavailable

b: Scheduled Sacrifice

c: Animal Found Dead

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105IP26

GROUP: 1-F
DOSE: 100 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

356	0.9	0.5	1.4
357	0.6	1.0	1.6
358	0.5	0.4	0.9
359	1.9	-0.1	1.8
360	0.9	0.6	1.5

MEAN	1.0	0.5	1.4
S.D.	0.55	0.40	0.34
N	5	5	5

--: Data Unavailable b: Scheduled Sacrifice

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105IP26

GROUP: 2-F
DOSE: 120 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

366	2.0	1.0	3.0
367	-0.2	1.3	1.1
368	1.3	-0.6	0.7
369	1.6	1.1	2.7
370	2.1	-0.2	1.9

MEAN	1.4	0.5	1.9
S.D.	0.93	0.86	0.99
N	5	5	5

--: Data Unavailable b: Scheduled Sacrifice

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105IP26

GROUP: 3-F
DOSE: 140 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

376	c	c	--
377	c	c	--
378	1.3	2.1	3.4
379	1.6	0.8	2.4
380	-0.4	1.0	0.6

MEAN	0.8	1.3	2.1
S.D.	1.08	0.70	1.42
N	3	3	3

--: Data Unavailable

b: Scheduled Sacrifice

c: Animal Found Dead

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105IP26

GROUP: 4-F
DOSE: 170 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

386	c	c	--
387	0.9	0.3	1.2
388	1.9	0.4	2.3
389	3.2	0.9	4.1
390	-0.3	1.2	0.9

MEAN	1.4	0.7	2.1
S.D.	1.49	0.42	1.45
N	4	4	4

--: Data Unavailable

b: Scheduled Sacrifice

c: Animal Found Dead

ACUTE INTRAPERITONEAL TOXICITY STUDY
OF WR269410 IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)

STUDY: 105IP26

GROUP: 5-F
DOSE: 200 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 7	DAY 14	TOTAL GAIN
----------	-------	--------	---------------

396	-1.4	3.0	1.6
397	c	c	--
398	1.2	1.2	2.4
399	c	c	--
400	c	c	--

MEAN	-0.1	2.1	2.0
S.D.	1.84	1.27	0.57
N	2	2	2

--: Data Unavailable

b: Scheduled Sacrifice

c: Animal Found Dead

APPENDIX 5

LD50 Data

ACUTE ORAL AND INTRAPERITONEAL TOXICITY
STUDY OF WR242511 AND WR269410 IN MICE

LD50 Data

WR242511 Tartrate (Gavage - Males)

PROGRAM NAME: LD50 VERSION 1, EFFECTIVE DATE 6/25/91

STUDY NUMBER	TEST ARTICLE	SPECIES	SEX
105PO24	1720614	MICE	MALE

AVERAGE # ANIMALS/SEX/GROUP	5
TOTAL ANIMALS USED	15
TOTAL ANIMALS USED 6.7%-93.3%	5

CALCULATIONS

Y-INTERCEPT	-16.51719
SLOPE	15.80134
16% CONCENTRATION	19.88137
50% CONCENTRATION	23.00023
84% CONCENTRATION	26.60835
T-VALUE	4.3
CORRELATION COEFFICIENT	.9938315

DATA SUMMARY

LEVEL	DOSE	LOG DOSE	# DEAD	% DEAD	PROBIT
1	17.00	1.23	0	0.0	3.04
2	23.00	1.36	2	40.0	4.75
3	30.00	1.48	5	100.0	6.96

THE LD50 FOR MALES IS 23 mg base/kg
THE 95% CONFIDENCE LIMITS 15.47 TO 34.19 mg base/kg

CALCULATION METHOD--MILLER AND TANTER
(PROC.SOC.EXP.BIO MED.,57:261-264,1944)

ACUTE ORAL AND INTRAPERITONEAL TOXICITY
STUDY OF WR242511 AND WR269410 IN MICE

LD50 Data

WR242511 Tartrate (Gavage - Females)

PROGRAM NAME: LD50 VERSION 1, EFFECTIVE DATE 6/25/91

STUDY NUMBER	TEST ARTICLE	SPECIES	SEX
105PO24	1720614	MICE	FEMALES

AVERAGE # ANIMALS/SEX/GROUP	5
TOTAL ANIMALS USED	15
TOTAL ANIMALS USED 6.7-93.3%	5

CALCULATIONS

Y-INTERCEPT	-16.46818
SLOPE	15.88871
16% CONCENTRATION	19.41876
50% CONCENTRATION	22.44705
84% CONCENTRATION	25.94759
T-VALUE	4.3
CORRELATION COEFFICIENT	.9993269

DATA SUMMARY

LEVEL	DOSE	LOG DOSE	# DEAD	% DEAD	PROBIT
1	17.00	1.23	0	0.0	3.04
2	23.00	1.36	3	60.0	5.25
3	30.00	1.48	5	100.0	6.96

THE LD50 FOR FEMALES IS 22.45 mg base/kg
THE 95% CONFIDENCE LIMITS 15.14 TO 33.29 mg base/kg

CALCULATION METHOD--MILLER AND TAINTER
(PROC.SOC.EXP.BIO MED.,57:261-264,1944)

ACUTE ORAL AND INTRAPERITONEAL TOXICITY
STUDY OF WR242511 AND WR269410 IN MICE

LD50 Data

WR242511 Tartrate (Intraperitoneal - Males)

PROGRAM NAME: LD50 VERSION 1, EFFECTIVE DATE 6/25/91

STUDY NUMBER	TEST ARTICLE	SPECIES	SEX
1051P24	1720614	MICE	MALE

AVERAGE # ANIMALS/SEX/GROUP	5
TOTAL ANIMALS USED	15
TOTAL ANIMALS USED 6.7%-93.3%	5

CALCULATIONS

Y-INTERCEPT	-16.41074
SLOPE	15.99084
16% CONCENTRATION	18.89741
50% CONCENTRATION	21.82419
84% CONCENTRATION	25.20426
T-VALUE	4.3
CORRELATION COEFFICIENT	.9789533

DATA SUMMARY

LEVEL	DOSE	LOG DOSE	# DEAD	% DEAD	PROBIT
1	17.00	1.23	0	0.0	3.04
2	23.00	1.36	4	80.0	5.84
3	30.00	1.48	5	100.0	6.96

THE LD50 FOR MALES IS 21.82 mg base/kg
THE 95% CONFIDENCE LIMITS 14.75 TO 32.29 mg base/kg

CALCULATION METHOD--MILLER AND TAINTER
(PROC.SOC.EXP.BIO MED.,57:261-264,1944)

ACUTE ORAL AND INTRAPERITONEAL TOXICITY
STUDY OF WR242511 AND WR269410 IN MICE

LD50 Data

WR242511 Tartrate (Intraperitoneal - Females)

PROGRAM NAME: LD50 VERSION 1, EFFECTIVE DATE 6/25/91

STUDY NUMBER	TEST ARTICLE	SPECIES	SEX
105IP24	1720614	MICE	FEMALES

AVERAGE # ANIMALS/SEX/GROUP	5
TOTAL ANIMALS USED	15
TOTAL ANIMALS USED 6.7-93.3%	5

CALCULATIONS

Y-INTERCEPT	-16.41074
SLOPE	15.99084
16% CONCENTRATION	18.89741
50% CONCENTRATION	21.82419
84% CONCENTRATION	25.20426
T-VALUE	4.3
CORRELATION COEFFICIENT	.9789533

DATA SUMMARY

LEVEL	DOSE	LOG DOSE	# DEAD	% DEAD	PROBIT
1	17.00	1.23	0	0.0	3.04
2	23.00	1.36	4	80.0	5.84
3	30.00	1.48	5	100.0	6.96

THE LD50 FOR FEMALES IS 21.82 mg base/kg
THE 95% CONFIDENCE LIMITS 14.75 TO 32.29 mg base/kg

CALCULATION METHOD--MILLER AND TAINTER
(PROC.SOC.EXP.BIO MED.,57:261-264,1944)

ACUTE ORAL AND INTRAPERITONEAL TOXICITY
STUDY OF WR242511 AND WR269410 IN MICE

LD50 Data

WR269410 (Intraperitoneal - Males)

PROGRAM NAME: LD50 VERSION 1, EFFECTIVE DATE 6/25/91

STUDY NUMBER	TEST ARTICLE	SPECIES	SEX
105IP26	1620614	MICE	MALE

AVERAGE # ANIMALS/SEX/GROUP	5
TOTAL ANIMALS USED	25
TOTAL ANIMALS USED 6.7%-93.3%	20

CALCULATIONS

Y-INTERCEPT	-10.46356
SLOPE	7.471125
16% CONCENTRATION	86.2835
50% CONCENTRATION	117.4293
84% CONCENTRATION	159.8177
T-VALUE	2.78
CORRELATION COEFFICIENT	.8743011

DATA SUMMARY

LEVEL	DOSE	LOG DOSE	# DEAD	% DEAD	PROBIT
1	100.00	2.00	1	20.0	4.16
2	120.00	2.08	4	80.0	5.84
3	140.00	2.15	3	60.0	5.25
4	170.00	2.23	4	80.0	5.84
5	200.00	2.30	5	100.0	6.96

THE LD50 FOR MALES IS 117.43 mg/kg
THE 95% CONFIDENCE LIMITS 89.56 TO 153.97 mg/kg

CALCULATION METHOD--MILLER AND TAINTER
(PROC.SOC.EXP.BIO MED.,57:261-264,1944)

ACUTE ORAL AND INTRAPERITONEAL TOXICITY
STUDY OF WR242511 AND WR269410 IN MICE

LD50 Data

WR269410 (Intraperitoneal - Females)

PROGRAM NAME: LD50 VERSION 1, EFFECTIVE DATE 6/25/91

STUDY NUMBER	TEST ARTICLE	SPECIES	SEX
105IM	1620614	MICE	MALE

AVERAGE # ANIMALS/SEX/GROUP	5
TOTAL ANIMALS USED	25
TOTAL ANIMALS USED 6.7%-93.3%	20

CALCULATIONS

Y-INTERCEPT	-10.46356
SLOPE	7.471125
16% CONCENTRATION	86.2835
50% CONCENTRATION	117.4293
84% CONCENTRATION	159.8177
T-VALUE	2.78
CORRELATION COEFFICIENT	.8743011

DATA SUMMARY

LEVEL	DOSE	LOG DOSE	# DEAD	% DEAD	PROBIT
1	100.00	2.00	1	20.0	4.16
2	120.00	2.08	4	80.0	5.84
3	140.00	2.15	3	60.0	5.25
4	170.00	2.23	4	80.0	5.84
5	200.00	2.30	5	100.0	6.96

THE LD50 FOR MALES IS 117.43 mg/kg
THE 95% CONFIDENCE LIMITS 89.56 TO 153.97 mg/kg

CALCULATION METHOD--MILLER AND TANTER
(PROC.SOC.EXP.BIO MED.,57:261-264,1944)

APPENDIX 6

Protocol and Amendments

ACUTE ORAL AND INTRAPERITONEAL TOXICITY
STUDY OF WR242511 AND WR269410 IN MICE

1.0 PURPOSE OF THE STUDY:

The purpose of this study is to assess the toxicity of the test articles in CD₁ mice following either a single oral or intraperitoneal dose.

2.0 SPONSOR:

2.1 Name: U.S. Army Medical Research
and Development Command

2.2 Address: Fort Detrick
Frederick, MD 21702-5009

2.3 Representative: George Schieferstein, Ph.D.

3.0 TESTING FACILITY:

3.1 Name: Toxicology Research Laboratory (TRL)

3.2 Address: University of Illinois at Chicago (UIC)
Department of Pharmacology
P.O. Box 6998
Chicago, Illinois 60680

3.3 Study Director: Barry S. Levine, D.Sc., D.A.B.T.

4.0 DATES:

4.1 Study Initiation (see Section; 12.0):

4.2 Proposed Initiation of Dosing: April 29, 1993 May 6, 1993
WR269410 WR242511

4.3 Proposed Necropsy Date: May 13, 1993 May 20, 1993

4.4 Proposed Study Completion
(Final Report): July 1, 1993

5.0 TEST ARTICLES

5A.1 Name or Code No: WR242511 Tartrate
Bottle number will be identified in the raw data.

5A.2 TRL Chemical No: 1720614

5A.3 Physical Description: Orange powder

5A.4 Stability and Handling of Test Article:

5A.4.1 Storage Conditions to Maintain Stability:

5A.4.1.1 Temperature: -20 to -15°C.

5A.4.1.2 Humidity: Ambient conditions at -20 to -15°C in a freezer.

5A.4.1.3 Light: Protect from light.

5A.4.1.4 Special Requirements: None.

5A.4.2 Special Handling Procedures: Standard precautions including gloves, labcoat and eye protection.

5A.4.3 Log of Test Article: The amount, date, identity of person(s) removing aliquots and the purpose for which each aliquot of the test article was removed from the batch will be documented. At termination of the study, all unused test article will be returned to the Sponsor.

5B.1 Name or Code No: WR269410 (p-Aminoheptanophenone; PAHP)
Bottle number will be identified in the raw data.

5B.2 TRL Chemical No: 1620614

5B.3 Physical Description: Solution in polyethylene glycol 200 in a concentration of 100 mg/ml.

5B.4 Stability and Handling of Test Article:

5B.4.1 Storage Conditions to Maintain Stability:

5B.4.1.1 Temperature: 0 to 4°C.

5B.4.1.2 Humidity: Ambient conditions at 0 to 4°C in the refrigerator.

5B.4.1.3 Light: Protect from light.

5B.4.1.4 Special Requirements: None.

5B.4.2 Special Handling Procedures: Standard precautions including gloves, labcoat and eye protection.

5B.4.3 Log of Test Article: The amount, date, identity of person(s) removing aliquots and the purpose for which each aliquot of the test article was removed from the batch will be documented. At termination of the study, all unused test article will be returned to the Sponsor.

6.0 PERSONNEL:

Study Director	Barry S. Levine, D.Sc., D.A.B.T.
Toxicologist	E. Marianna Furedi-Machacek, D.V.M.
Analytical Chemist	Adam Negrusz, Ph.D.
Clinical Veterinarian	James Artwohl, D.V.M., M.S., D.A.C.L.A.M.
Veterinarian Support	To be documented in the raw data
Tox. Lab Supervisor	Soudabeh Soura, B.S.
Lead Technician	Nancy Dinger, B.S.
Chemistry Specialist	Thomas Tolhurst, B.S.
Quality Assurance	Ronald C. Schoenbeck

7.0 TEST SYSTEM:

- 7.1 Species: Mouse
- 7.2 Strain: CD₁ (Virus Antibody Free)
- 7.3 Sex(s) and Number: 100 Males and 100 females for LD50 test.
Up to 40/sex for the range-finding test.
- 7.4 Age of Animals: 6 - 7 weeks old at dosing initiation.
- 7.5 Weight of Animals: Approximately 27 - 32 g (males) and \approx 22 - 26 g (females) at dosing initiation.
- 7.6 Source of Animals: Charles River Breeding Laboratories. The specific breeding facility will be documented in the raw data.
- 7.7 Justification for Selection of Test System: The mouse is a standard and accepted rodent species for toxicology studies, and is specified by the Sponsor.
- 7.8 Procedure for Unique Identification of Test System: Upon arrival, each animal will be given a study-unique quarantine/pretest number. During the test animal selection process, each test animal will be assigned a test animal number unique to it within the population making up the study. This number will appear as an ear tag and will

also appear on a cage card visible on the front of each cage. The cage card will additionally contain the study number, test article identification, treatment group number and dose level. Cage cards will be color-coded as a function of treatment group. Raw data records and specimens will also be identified by the unique test animal number.

- 7.9 Housing: The animals will be housed in an AAALAC-accredited facility. Animals will be singly housed in polycarbonate cages with Anderson-bed-o-cob bedding (Heinold, Kankakee, Illinois) in a temperature (65-78°F) and humidity (30-70%) controlled room with a 14 hour light/10 hour dark cycle. The cage size, 390 cm area and 12.5 cm height, is adequate to house mice at the upper weight range as described in the Guide for the Care and Use of Laboratory Animals, DHHS (NIH) No. 86.23. All animals will be routinely transferred to clean cages with fresh bedding once weekly.
- 7.10 Quarantine Procedure: Animals for the LD50 study will be quarantined for an approximate one week period. The range-finding test will start before the end of the quarantine period. During quarantine, the animals will be observed daily for signs of illness, and all unusual observations will be reported to the Study Director, Toxicologist or Clinical Veterinarian. Animals will be examined during quarantine and approved for use by the Clinical Veterinarian prior to being placed on test. Any sickly animals will be eliminated prior to the test animal selection process. If a selected animal appears sickly prior to initiation of treatment, it will be replaced by a healthy animal prior to initiation of treatment under the direction of the Study Director or Toxicologist. Quarantine release will be documented on the Clinical Veterinarian Log by the veterinarian prior to study initiation.
- 7.11 Food: Purina Certified Rodent Chow No. 5002 (Ralston Purina Company, St. Louis, MO) will be provided *ad libitum* from arrival until termination except for an approximate 3-6 hour fast prior to gavage treatment. Food will be returned 1-2 hours post treatment.
- 7.12 Water: Tap water from an automatic watering system in which the room distribution lines are flushed daily will be provided *ad libitum* from arrival until termination. The water is untreated with additional chlorine or HCl.
- 7.13 There are no known contaminants in the feed or water which are expected to influence the study. A copy of the feed certification will be kept with the study records. The results of bimonthly comprehensive chemical analyses of Chicago water are documented in files maintained by Quality Assurance.

8.0 EXPERIMENTAL DESIGN:

8.1 LD50 Test:

<u>Test Article</u>	<u>Dose Level (mg base/kg)^a</u>	<u>Route of Administration</u>	<u>Number of Males</u>	<u>Number of Females</u>
WR269410	TBD	Oral	5	5
WR269410	TBD	Oral	5	5
WR269410	TBD	Oral	5	5
WR269410	TBD	Oral	5	5
WR269410	TBD	Oral	5	5
WR269410	TBD	Intraperitoneal	5	5
WR269410	TBD	Intraperitoneal	5	5
WR269410	TBD	Intraperitoneal	5	5
WR269410	TBD	Intraperitoneal	5	5
WR269410	TBD	Intraperitoneal	5	5
WR242511	TBD	Oral	5	5
WR242511	TBD	Oral	5	5
WR242511	TBD	Oral	5	5
WR242511	TBD	Oral	5	5
WR242511	TBD	Oral	5	5
WR242511	TBD	Intraperitoneal	5	5
WR242511	TBD	Intraperitoneal	5	5
WR242511	TBD	Intraperitoneal	5	5
WR242511	TBD	Intraperitoneal	5	5
WR242511	TBD	Intraperitoneal	5	5

^aTBD = To be determined (WR242511 doses will be expressed as mg base per kg).

Additional dose levels will be included as necessary to more accurately define the LD50. The number of animals in each group is necessary for statistical analyses.

Doses will be selected from range-finding study data in which 5 groups of 2 animals/sex/dose will be routinely used (Section 8.6).

- 8.2 Procedure to Control Bias during the Assignment of Animals to Treatment Groups: The animals will be randomly selected, within sex, using a table of random numbers or a computer-generated randomization program. The specific procedure will be documented in the raw data.

- 8.3 Frequency and Route of Administration of Test Article: Five groups of five animals/sex will receive a single dose of the appropriate test article by intraperitoneal injection or gavage as shown in Section 8.1. Dosing volumes will be constant on the basis of body weight and will be routinely 1 or 5 ml/kg (ip), and 5 or 10 ml/kg (oral). The specific dosing volume (ml/kg) will be constant throughout each phase of the study and will be documented in the raw data. Mice which are dosed by gavage will be fasted approximately 3 - 6 hours prior to dosing. Food will be returned approximately 1 - 2 hours after dosing.
- 8.4 Justification of Route(s): The oral and intraperitoneal routes are convenient and accepted procedures for administering a specific amount of a test article to each animal, and are required by the Sponsor.
- 8.5 Test Article Vehicle: WR242511 - 1% Methylcellulose/0.4% Tween 80
WR269410 - Polyethylene glycol (PEG) 200, supplied by the University of Iowa
- 8.6 Range-Finding Test: For WR242511, an initial range-finding dose of 25 mg base/kg will be administered orally and intraperitoneally to separate groups of 2 animals/sex. This dose is approximately the oral LD50 determined in a previously conducted acute toxicity study in mice (UIC/TRL Study No. 061). For WR269410, an initial range-finding dose of 800 mg/kg will be used for each route (2 animals/sex). This is the approximate intramuscular LD50 for this drug in mice as indicated by the Sponsor.
- Additional range-finding dose levels, routinely either twice or one-half the previous dose level, will be subsequently administered to groups of 2 animals/sex/appropriate route based on the previous results. Five range-finding doses/sex will be routinely administered for each drug by the appropriate route. The range-finding animals will be observed once daily for at least 5 days, and will be discarded when it is apparent they will survive.
- 8.7 Test Article Dosage Form Preparation and Analyses: The stability and homogeneity of the test article/carrier mixtures will be determined prior to study start. Dosage formulations will be prepared by suspending the appropriate quantity of test article in the vehicle using a mortar and pestle. They will be analyzed for test article concentration prior to use, and only samples within 10% of their intended concentration will be used. A stock solution of WR269410 in PEG 200 (100 mg/ml) will be prepared and supplied by the University of Iowa. Appropriate quantities of the stock solution will be further diluted in PEG 200 for each dose level. The final dosage formulations used in the LD50 test will be returned to the University of Iowa for test article concentration assay.
- 8.8 Type and Frequency of Observations, Tests, Analyses and Measurements:
- 8.8.1 Body Weight: Body weights of all animals will be recorded at test animal selection in Week -1, and on Days 0 (prior to dosing), 7 and 14.

8.8.2 Clinical Signs: All test animals will be observed for clinical signs at least three times after treatment on the day of dosing, and daily thereafter until termination. All pharmacologic and/or toxicologic effects will be recorded on an individual test animal basis. The animals will also be observed daily in the afternoon for moribundity/mortality during the 2 week holding period.

8.8.3 Postmortem Observations: All test animals which die during the 14-day observation period will be grossly necropsied as soon as possible. Those test animals that survive to Day 14 will be sacrificed by carbon dioxide asphyxiation and grossly necropsied on that day. The necropsy procedure will be a thorough and systematic examination and dissection of the animal viscera and carcass. A veterinary pathologist will be routinely available to verify gross lesions. All tissues and organs will be discarded following termination of the gross necropsy procedure.

8.8.4 Data Analyses: The incidence of all pharmacologic and/or toxicologic effects will be tabulated for each dose level by sex. For body weights, means and standard deviations will be calculated for each dose level by sex and time point. Probit analysis of dose-mortality data as described by Finney (1977) will be used to calculate the LD50 and its 95% confidence interval for each sex, and the slope of each dose-mortality curve.

9.0 RECORDS TO BE MAINTAINED:

All data generated during the conduct of the study, except those that are generated as direct computer input, will be recorded directly, promptly, and accurately in ink in bound books with prenumbered pages or on worksheets that will be bound during or at the conclusion of the nonclinical laboratory study. All appropriate computer and machine output will be bound during or at the conclusion of the study. All data entries will be dated on the day of entry and signed or initialed by the person entering the data.

Any changes in entries for whatever reason (e.g., to correct an error or transposition) will be made so as not to obscure the original entry, will indicate the reason for such change, and will be dated and signed or identified at the time of data input. In computer driven collection systems, the operator responsible for direct data input will be identified at the time of data input. Any changes in computer entries for whatever reason (e.g., to correct an error or transposition) will be made in such a manner so as not to obscure the original entry, if possible, will indicate the reason for such change, and will be dated and the responsible individual will be identified.

All recorded data will be reviewed, signed, and dated by a knowledgeable person, other than the person making the entry, to assure adherence to procedures and to verify observations.

Upon completion of the study and submission of the final report, all raw data, documentation, specimens, test article reserves and other materials necessary to reconstruct the study will be stored in the TRL Archives maintained by Quality Assurance, unless otherwise specified by the Sponsor.

All changes or revisions, and reasons therefore, to this protocol once it is approved will be documented, signed by the Study Director and Sponsor, dated and maintained with the protocol.

10.0 REGULATORY REQUIREMENTS:

This study will be performed in compliance with the UIC/TRL Quality Assurance Program designed to conform with FDA Good Laboratory Practice Regulations and EPA Good Laboratory Practice Standards. The protocol for this study was approved by the UIC Animal care committee.

Will this study be submitted to a regulatory agency? Yes
If so, to which agency(ies)? U.S. Food and Drug Administration
Does the Sponsor request that remaining test articles be returned? Yes
Does the Sponsor request that samples of the test article/carrier mixture(s) be sent? No

11.0 REFERENCES

Finney, D.J., 1977. Probit Analysis, 3rd Edition. Cambridge University Press, Cambridge, England.

12.0 PROTOCOL APPROVAL:

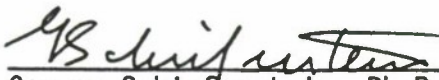
STUDY DIRECTOR:


Barry S. Levine, D.Sc., D.A.B.T. 12/3/92
Date

QUALITY ASSURANCE:


Ronald Schoenbeck 12/7/92
Date

SPONSOR APPROVAL:


George Schieferstein, Ph.D.
Contracting Officer's
Representative (COR) 12/8/92
Date

COMMENTS FROM THE COR:

PROTOCOL AMENDMENT

Study No.: 105

Title: Acute Oral and Intraperitoneal Toxicity Study of WR242511 and WR269410 in Mice

1. Page 1 Section 4.0

Complete the study dates as follows:

4.2 <u>Proposed Initiation of Dosing:</u>	April 29, 1993 WR269410	May 6, 1993 WR242511
4.3 <u>Proposed Necropsy Date:</u>	May 13, 1993	May 20, 1993
4.4 <u>Proposed Study Completion</u> <u>(Final Report):</u>	July 1, 1993	

Reason: The dates were not specified in the Protocol.

2. Page 2 Section 5A.2

Change TRL Cemical No. "0930614" to "1720614"

Reason: A different composition of the test article was supplied by the Sponsor (tartarate instead of disulfate which was previously tested and was assigned number 0930614).

3. Page 2 Section 5B.3

Change "White powder" to "Solution in polyethylene glycol 200 in a concentration of 100 mg/ml"

Reason: Because of difficulties with test article solubility, it was supplied by the Sponsor as a solution.

4. Page 2 Secion 5B.4.1.1 and 5B.4.1.2

Add 0 - 4°C for solution in the refrigerator.

Reason: PEG 200 solutions of WR269410 do not need to be frozen.

5. Page 3 Section 6.0

A. Change the Analytical Chemist to Adam Negrusz, Ph.D."

B. Change "Veterinary Support" to "Veterinarian Support"

Reason: Mistakes in protocol.

PROTOCOL AMENDMENT

Study No.: 105

Title: Acute Oral and Intraperitoneal Toxicity Study of WR242511 and WR269410 in Mice

6. Page 3 Section 7.3

Change the number of mice used for the range-finding test from "Up to 20/sex" to "Up to 40/sex".

Reason: Mistake in protocol.

7. Page 4 Section 7.9

A. Change animal room humidity range from "(40-70%)" to "(30-70%)" in the second sentence.

B. Change "DHEW" to "DHHS" in the third sentence.

Reason: Mistakes in protocol.

8. Page 4 Section 7.11

Add to the end of the last sentence "except for an approximate 3-6 hour fast prior to gavage treatment. Food will be returned 1-2 hours post treatment."

Reason: Inadvertently omitted from the protocol.

9. Page 4 Section 7.12

Change "HCL" to "HCl" at the end of last sentence.

Reason: Mistake in protocol.

10. Page 5 Section 8.1

Add the following sentence to the beginning of the first paragraph:

"Additional dose levels will be included as necessary to more accurately define the LD50."

Reason: To allow for additional dose levels as necessary.

11. Page 6 Section 8.5

A. Change the test article vehicle for WR242511 from "0.5% Na⁺ Carboxymethylcellulose/0.3% Tween 80" to "1% Methylcellulose/0.4% Tween 80."

Reason: Better suspendability was achieved with this vehicle.

PROTOCOL AMENDMENT

Study No.: 105

Title: Acute Oral and Intraperitoneal Toxicity Study of WR242511 and WR269410 in Mice

B. Change the test article vehicle for WR269410 from "0.5% Na⁺ Carboxymethylcellulose/0.3% Tween 80" to "Polyethylene glycol (PEG) 200, supplied by the University of Iowa."

Reason: WR269410 in suspension could not be passed through a needle.

12. Page 6 Section 8.6

Add "base" to the first sentence to read as follows: For WR242511, an initial range-finding dose of 25 mg base/kg will be administered..."

Reason: Inadvertently not included in the protocol.

13. Page 6 Section 8.7

Add the following sentences at the end of the paragraph:

"A stock solution of WR269410 in PEG 200 (100 mg/ml) will be prepared and supplied by the University of Iowa. Appropriate quantities of the stock solution will be further diluted in PEG 200 for each dose level. The final dosage formulations used in the LD50 test will be returned to the University of Iowa for test article concentration assay."

Reason: Difficulties were encountered in preparation of dosage formulation suspensions.

APPROVALS:

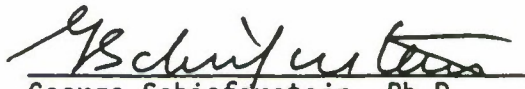
STUDY DIRECTOR:



Barry S. Levine, D.Sc., D.A.B.T.

5/27/93
Date

SPONSOR APPROVAL:



George Schieferstein, Ph.D.
Contracting Officer's
Representative (COR)

6/3/93.
Date

APPENDIX 7
Study Deviations

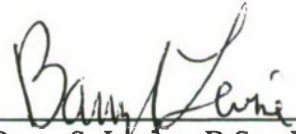
ACUTE ORAL AND INTRAPERITONEAL TOXICITY
STUDY OF WR242511 AND WR269410 IN MICE

Study Deviations*

<u>Deviation Type</u>	<u>Specific Deviation</u>	<u>Effect on Study</u>
Protocol	The method of Miller and Tainter (1944) was used to calculate LD50s because it is an accepted means to analyze dose-mortality curves and it is able to perform linear regression with one only data point between 0% and 100% mortality.	None.
Protocol	WR242511 tartrate is incorrectly described in the protocol as an orange powder. The tartrate salt of WR242511 is a yellow powder.	None.
Protocol	The humidity in the animal room was out of range on two occasions ($\pm 1\%$ out of range).	None; deviation was minimal.
Protocol	The WR269410 (intraperitoneal) dosage formulation for the mid dose (140 mg/kg) treatment group exceeded the target concentration by 11.8%.	None; deviation was minimal.

*The detailed "Deviation Reports" are contained in the raw data which are archive at the University of Illinois at Chicago, Department of Pharmacology, Chicago, Illinois.

The above deviations did not affect the integrity of the study.


Barry S. Levine, D.Sc., D.A.B.T.
9/9/93
Date